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Original article

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Nosocomial Outbreak of 2019 Novel Coronavirus Pneumonia in Wuhan, China

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ABSTRACT

Background

The novel coronavirus (SARS-CoV-2) infected over 3,300 health-care-workers (HCWs) in early 2020 in China. Little information is known about nosocomial infections of HCWs in the initial period. We analyzed data from HCWs with nosocomial infections in Wuhan Union Hospital and their family members.

Methods

We collected and analyzed data on exposure history, illness timelines, and epidemiologic characteristics of 25 laboratory-confirmed and two highly suspected HCWs as well as ten of their family members with COVID-19 from Jan 5 to Feb 12, 2020. Among them, demographics and clinical features of the 35 laboratory-confirmed cases were investigated and viral RNA of 12 cases was sequenced and analyzed.

Results

Nine clusters were found among the patients. All patients showed mild to moderate clinical manifestation and recovered without deterioration. The average periods of incubation, clinical onset serial interval (COSI), and virus shedding were 4.5 days, 5.2 ± 3.2 days, and 18.5 days, respectively. Complete genomic sequences of 12 different coronavirus strains demonstrated that the viral structure with small, irrelevant mutations was stable in the transmission chains and showed remarkable traits of infectious traceability.

Conclusions

SARS-CoV-2 can be rapidly transmitted person-to-person regardless of whether they have symptoms in both hospital settings and social activities based on the short period of incubation and COSI. The public health service should take practical measures to curb the spread, including isolation of cases, tracing close-contacts, and containment of severe epidemic areas. Besides, the HCWs should be alert during the epidemic, and make self-quarantine if self-suspected.

INTRODUCTION

Seventeen years after the 2003 epidemic of severe acute respiratory syndrome (SARS) [1,2], a novel coronavirus, SARS-CoV-2, was isolated from bronchoalveolar lavage of several patients with unknown origin pneumonia in Wuhan City, China[3]. SARS-CoV-2 has caused the coronavirus disease 2019 (COVID-19) across the country and abroad. A total of 83,157 COVID-19 cases with 4.02% mortality has been reported in China up to April 7, 2020[4]. The confirmed cases have been identified in more than 180 countries and regions around the world, and more than 1,300,000 people have been infected globally outside China, including 78,932 deaths[5]. The hunt for patient zero is critical, but epidemiological investigations are often complex and unclear[6]. A COVID-19 patient usually presents with fever, a non-productive cough, myalgia, and malaise. Symptoms, including a productive cough and headache, are less common. Dyspnea is observed in more than one-fourth of patients. Cases with persistent lymphopenia usually develop fatal comorbidities, including acute respiratory distress syndrome (ARDS), acute cardiac injury,

secondary infection and multiorgan dysfunction [7-9].

SARS-CoV-2 is a positive-sense and single-stranded RNA virus of zoonotic origin belonging to Betacoronavirus lineage B[3]. It has successfully crossed the animal-to-human barrier and proved to be capable of epidemic spread and may even have endemic persistence in the human population[10]. The calculated R0 of SARS-CoV-2 is as high as 2.68[11], making prevention measures and intervention tactics very challenging. Unfortunately, current general hospital settings in Wuhan and many other cities are acting as epidemic hot spots to facilitate transmission and exacerbate spread[12]. So far, over 3,300 health-care workers (HCWs) in China have been diagnosed as infected mainly through nosocomial transmission[13]. HCWs are the first to suffer during the epidemic. The transmission dynamics of COVID-19 in hospitals in the initial period, especially among HCWs, are important to deeply understand epidemiology of the diseases.

Here we investigated possible transmission links by integrating epidemiological data and whole-genome sequencing (WGS) of 25 HCWs and two highly suspected HCWs as well as their family members who got successively infected with SARS-CoV-2 in the initial period in Wuhan Union Hospital. We also collected and analyzed the clinical data of 35 laboratory-confirmed cases of these individuals.

METHODS

Study design and participants

A total of 35 laboratory-confirmed cases and two highly suspected cases were

enrolled between Jan 5 to Feb 12, 2020, including 27 HCWs and ten relatives out of seven families. All participants were interviewed using a standard questionnaire that elevated communicable diseases. Items such as HCWs' contact history with the confirmed COVID-19 patients, including where, when, and how they had been exposed, were assessed. We mapped all cases with the precise time of symptom onset. Clusters outbreaks, potential exposures and possible patterns of transmission were estimated.

We collected clinical data of 35 laboratory-confirmed cases, including symptoms and signs, laboratory examinations, chest imaging, comorbidities and complications, and clinical treatment and outcomes, which were arranged using a standardized data collection form referencing the case record form shared by the International Severe Acute Respiratory and Emerging Infections Consortium(ISARIC)[14] and the Household transmission investigation protocol for 2019-novel coronavirus (SARS-CoV-2) infection from the World Health Organization[15].

Real-Time Reverse Transcription polymerase chain reaction assay to detect SARS-CoV-2

The SARS-CoV-2 laboratory test assays were based on the previous WHO recommendation[16]. RNA was extracted from oropharyngeal swabs of patients suspected of having SARS-CoV-2 infection using the respiratory sample RNA isolation kit. Then real-time reverse transcription-polymerase chain reaction (RT-PCR) assay of SARS-CoV-2 RNA was conducted to amplify and test two target

genes, including open reading frame1ab (ORF1ab) and nucleocapsid protein(N). Details of the manufacturer's protocol for RNA extraction, RT-PCR assay and the diagnostic criteria are illustrated in the Supplementary Appendix.

Whole-genome sequencing and comparative genome analysis

Nasopharyngeal and/or oropharyngeal swabs were obtained from all COVID-19 cases for SARS-CoV-2 nucleic acid assay, and 22 of them were processed using whole-genome sequencing (WGS). Full genomes were sequenced using the BioelectronSeq 4000 (CapitalBio Corporation, Beijing) and assembled using the *de novo* genome assembler, SPAdes[17], version 3.10.1, software. The complete genome was annotated by Prokka[18], version 1.14.5, software. The mutations were analyzed with the use of Sibelia[19], version 3.07, software, based on existing Wuhan-Hu-1 (NC_045512.2) genome and were annotated by SnpEff[20], version 4.3, software. We integrated information from 60 published genomic sequences of SARS-CoV-2.

Full-length genomes were combined with published SARS-CoV-2 genomes and other coronaviruses and aligned using FFT-NS-2 model by MAFFT[21], version 7.455. Maximum-likelihood phylogenies were inferred under a generalized-time-reversal (GTR)+ Gamma substitution model and bootstrapped 1000 times to assess confidence using RAxML[22], version 8.2.12. The mutations of assembled amino acid sequences of Spike protein were compared with Wuhan-Hu-1 (NC_045512.2), bat-SL-CoVZC45 (MG772933.1), and SARS coronavirus isolate Tor2/FP1-10851 (JX163927.1) using Clustal Omega[23].

Epidemiological analysis

For participants with detailed onset information, a log-normal distribution was used to fit the incubation period and the probability distribution of the incubation period was estimated. For participants with detailed medical visit information, the Weibull distribution was used to fit and determine onset-to-first-medical-visit and onset-to-admission distributions on the dates of the onset of the illness, first medical visit and hospital admission. The clinical onset serial interval (COSI) was calculated, for which the probability distribution was estimated by the gamma distribution.

Statistical analysis

For clinical data, categorical variables were expressed as number (proportion). Continuous variables were expressed as median and compared by Mann-Whitney U tests. P values less than 0.05 were considered significant. Statistical analyses were conducted using SPSS software, version 23.0 (IBM Corp., Armonk, NY, USA), unless otherwise indicated.

Ethical Approval

Ethical approval was waived by the institutional review board of the hospital since we collected and analyzed all data from the patients according to the policy for public health outbreak investigation of emerging infectious diseases issued by the National Health Commission of the People's Republic of China.

RESULTS

Nosocomial outbreak of novel coronavirus pneumonia and its epidemiologic transmission patterns

One male patient (69 years old) in the Department of Neurosurgery of Wuhan Union Hospital developed a fever of 38 °C on Jan 6, 2020 and was finally diagnosed as COVID-19 on Jan 16, 2020. Another female patient (55 years old) had a fever on Jan 11, 2020, and was confirmed on Jan 18, 2020. During this period, the HCWs in the Department of Neurosurgery either had direct contacts with the two index patients without sufficiently efficient personal protective equipment, or they had indirect contacts through their co-workers in the department gatherings on Jan 12 and 13, 2020. Twelve of the HCWs in the Department of Neurosurgery were finally diagnosed as laboratory-confirmed COVID-19, from Jan 16 to Jan 24, 2020. Besides, two HCWs (O and Z) were diagnosed as probable case with similar clinical manifestations but negative viral nucleotide tests. Beyond the Department of Neurosurgery, there were 13 HCWs of other departments were laboratory-confirmed COVID-19 cases. These departments also had suspects enrolled at the same time.

After the 25 HCWs' onset of illness, ten out of 43 family members were confirmed as COVID-19 cases via nucleotide tests. The remaining 33 family members of HCWs were not secondary infected, because of these HCWs' taking strict self-quarantine strategies immediately after their onsets of illness, including wearing

a facial mask when they came home, living alone in a separated room, never eating together with families, etc. In a word, from Jan 5 to Jan 29, 2020, 25 HCWs and ten family members out of seven families were diagnosed as COVID-19 in a single hospital. A detailed epidemiological and contact history, as well as cluster information were shown in Supplementary Appendix. The time distribution of symptom onset and speculative transmission pattern were shown in Figure 1A and Figure 1B, respectively.

Transmission, incubation period, and serial interval

According to the information of 14 laboratory-confirmed cases who had specific dates of exposure and symptom onset, we estimated that the average incubation period is 4.5 days (95% CI, 3.0-6.4). The 95th percentile of the probability distribution for the incubation period was 11.4 days (95% CI, 4.0-12.0) (Figure 2A). Through the nine transmission chains (Figure 1B), we estimated that the COSI distribution is 5.2 ± 3.2 days (95% CI, 3.8-6.8) (Figure 2B). Among the data obtained from 35 confirmed cases (including the HCWs and their family members) and two suspected cases, the interval from the date of onset to the first medical visit was estimated to have a mean of 3.0 days (95% CI, 2.2-3.9) (Figure 2C). Of the 27 hospitalized cases (23 HCWs and 4 family members), the interval from the date of onset to hospital admission was estimated to have a mean of 6.6 days (95% CI, 5.3-8.2) (Figure 2D). There were no significant differences in these four indicators between HCWs and their family members.

Demographic and clinical features in 35 confirmed cases

The clinical outcomes of the patients are shown in Table 1. Among 35 confirmed cases, 22 (62.9%) were women, and the median age was 37 (Range, 25 to 88). A few patients had underlying diseases, including hypertension (11.4%), coronary heart disease (2.9%), diabetes (5.7%), and asthma (5.7%). Up to Feb 12, 2020, a total of 21 patients (60%) had recovered and been discharged from hospital, six patients (17.1%) requiring medical observation remained in hospital, and eight patients (22.9%) who stayed home under self-quarantine had recovered. The median of virus shedding time was 18.5 days (Range, 12 to 25 days). The median time for the length of hospital stay was 21 days (Range, 13 to 28 days).

The most common signs and symptoms on admission were fever (85.7%) and malaise (74.3%), 22 (62.9%) of patients had a poor appetite, and 19 (54.3%) of the patients had a cough. Six patients received oxygen therapy because of hypoxemia. Corticosteroids were not administrated in any patients. (Table S1 in the Supplementary Appendix).

The laboratory results of patients are shown in Table S2 in the Supplementary Appendix. The complete blood counts of patients on admission showed that the number of white blood cells was normal in most patients (27/31, 87.1%), 13 of the 30 patients (43.3%) had lymphopenia, alanine aminotransferase was abnormal in 4 patients (15.4%). Creatinine was normal in all patients. Seven patients (30.4%) had increased lactate dehydrogenase.

On admission, infiltrations in chest computed tomography (CT) images were detected in most the cases. In total, 29 of them (82.9%) showed ground-glass opacities (GGO), four of them (11.4%) showed consolidations, one of them (2.9%) presented mixed GGO and consolidation. Only one patient (2.9%) had normal chest imaging (Table S2 in the Supplementary Appendix). We showed two series of typical CT images of moderate pneumonia (HCW A and C, Figure 3) and a series of CT images of a suspected case (HCW O, Figure S5).

Sequencing and phylogenetic analysis

We obtained 12 whole-genome sequences (GenBank accession numbers: MT079843-MT079854) after implementing *de novo* sequencing from 22 swab specimens from 22 COVID-19 patients. These patients were B, C, E, F, G, H, J, M, Q, R, V, and e as shown in Figure 1B, and their corresponding sample numbers were summarized in Table S3 in the Supplementary Appendix. The remaining ten samples were removed due to insufficient coverage of the extracted virus genome. Compared with Wuhan-Hu-1, except for V, the remaining 11 viral genomes all have two nucleotide mutations. We found these two mutation sites both exist in 16 (26.2%) published virus genomes (Table S4-6 in the Supplementary Appendix). V showed two missense mutations completely different from the other 11 cases, mainly because he has been exposed to many other patients' clinical specimens due to his daily job. The sequences from R and her husband e, are the same (Figure 4A). A total of six missense mutations were found in the 12 genomes of SARS-CoV-2

strains, but none of them were located in the genes for structural proteins in the new coronavirus, including S, E, M or N proteins (Figure 4A). Five of the mutations were located on the non-structural proteins (nsp), which are hydrolyzed from the virus-encoded polyproteins 1a/1ab1. The one remaining missense mutation (28144^{th} T > C) was located on the cofactor gene ORF8.

The phylogenetic tree of full-length genomes showed that SARS-CoV-2 strains form a monophyletic clade with a bootstrap support of 100% (Figure S3 in the Supplementary Appendix). The most closely related sequence to this clade is bat-SL-CoV. Sequences from six HCWs (C, H, J, M, Q, R) in the Department of Neurosurgery and one family members e were closely related in the phylogenetic tree (Figure 4B). The sequence from HCW B in another department was formed a separate lineage. Compared with bat-SL-CoVZC45 (MG772933.1) and SARS coronavirus isolate Tor2/FP1-10851 (JX163927.1), SARS-CoV-2 had four and three insertion regions respectively (Figure 4C).

DISCUSSION

Given the outbreak event of COVID-19 in Wuhan City and Hubei Province in China, we lacked efficient viral identification capacity to diagnose probable COVID-19 cases at the very early stage. There were no effective prevention measures in general hospital settings to isolate and manage the suspected COVID-19 cases, or to valid containment measures to block the transmission pathways[12]. HCWs are the highest risk occupational population in such acute respiratory infectious diseases, such as

SARS and COVID-19, transmitted by contact or respiratory droplets, aerosols or fomites[24]. Here, we describe several clusters of COVID-19 cases in a hospital, by person-to-person transmission of SARS-CoV-2 to assess the epidemiological features of COVID-19.

We reported 25 laboratory-confirmed and two highly suspected HCWs, infected successively in Wuhan Union Hospital, 14 of whom were co-workers in the Department of Neurosurgery, including two clusters with two index patients as the sources, which further emphasized the importance of adequate protection for HCWs during their daily work. Moreover, seven family clusters associated with these HCWs have occurred, mainly due to the close contacts between the affected HCWs and their family members without any isolation measures. Fortunately, the majority of HCWs who isolated themselves from their family members at the onset of illness, effectively protected their family members from getting infected. Through mapping the time of onset and possible routes of transmission (Figure 1B), we can conclude that the general hospitals are just like an epidemic hub gathering a lot of patients who are the sources of infection, which would efficiently facilitate and exacerbate the transmission and spreading of virus via public transportation or alternative ways.

Through the phylogenetic analysis, we found clustered cases that were closer in the phylogenetic tree (Figure 4B). Mutation analysis showed that the sequence from each sample had different mutation sites, most of which were synonymous mutation. Even if some missense mutations existed, none of them were located in the genes for structural proteins of SARS-CoV-2 (Figure 4A). Additionally, the amino acid

sequences of the structural proteins had no changes (Figure S1, Figure S2 in the Supplementary Appendix).

Most of the initial symptoms in our cases were myalgia/malaise and fever. Some patients had no fever but only mild symptoms such as nasal congestion, which may lead to patients being overlooked, causing a wider spread of COVID-19. In our cases, the intervals of onset of illness to the first medical visit and onset of illness to hospital admission were estimated to have a mean of 3.0 days and 6.6 days, respectively, which were shorter than in other studies[25]. By Feb 12, 21 of 27 hospitalized cases (77.8%) were recovered and discharged, none of them were admitted to the ICU or died. From the chest CT images from HCW A and C, very mild or moderate infiltrations were presented and became alleviated and resolved significantly in a short time (Figure 3). So, early diagnosis, isolation and timely treatments can speed up the recovery of patients and decrease the deteriorative tendency.

The median time for virus shedding to become negative in our cases was a long period of 18.5 days (Range, 12 to 25 days). It is worth mentioning that Nurse F was attacked by severe diarrhea during hospitalization. Even after the nucleic acid test of nasopharynx swabs turned negative and lung CT images got better, the viral nucleic acid test of stool maintained a sustainable positive one month after onset. We must thus pay close attention to the status of virus clearance of patients with COVID-19. Such a long virus shedding period perhaps highlights the production of efficiently neutralizing antibodies in a comparatively postponed manner or even an

unsatisfactory titter in the patient's plasma. Therefore, it might be necessary to extend the period of hospitalization for infectious control purposes, and we should adopt a prudent strategy for treating critical severe patient with convalescent plasma from COVID-19 patients.

Our current study has some limitations. First, the potential bias of the incubation period and COSI in our study might account for only 37 patients enrolled. The more accurate incubation period and COSI need further verification through a larger sample size. Second, the implementation of the kinetics of virus shedding and the relevant viral loading in both respiratory and intestinal tracts was not available since the novel causative pathogen has just been identified. Third, the potential for superficial exposure in infection transmission was not investigated, which may need further studies. Fourth, the kinetics of viral antibody, especially the neutralized antibody, were not monitored due to laboratory limitations. Finally, viral genome analysis and traceability from each patient have not been performed and should be conducted in future studies.

In summary, similar to the 2003 SARS outbreak in Guangzhou, the current epidemic of SARS-CoV-2 resulting in COVID-19 in Wuhan is mainly due to efficient person-to-person transmission or super-spreading events in hospital settings and social activity based on the short period of incubation and COSI. Practical strategies and measures, such as isolation of patients, tracing and quarantine of close contacts and containment of severe epidemic areas, are crucial to block the spread. Earlier detection and diagnosis of patients with COVID-19 will result in better prognoses.

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Contributors

ZG and WM had the idea for and designed the study and had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. XRW, YH, LBL, and XM contributed to drafting the manuscript. ZG, XRW, YZ, QZ, HS, and WM contributed to critical revision of the manuscript for valuable intellectual content. YH, LBL, LML, and XM conducted the statistical analysis. TD, YG, BZ, WL, XB, TP, GW, YC, and ZZ contributed to the sequencing and bioinformatics analysis. XRW, QZ, XSW, NCJ, LM, DY, JZ, BY, YX, and NJ

contributed to data acquisition, data analysis, or data interpretation. The final version had been reviewed and approved by all authors.

Declaration of interests

No competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Table 1. Epidemic Characteristics and Clinical Outcomes of Patients of HCWs and their family members with Laboratory-Confirmed Novel Coronavirus Pneumonia

Variable	HCWs (N=25)	HCW's family members (N=10)	Total (N=35)
Female sex — no. (%)	17(68)	5(50)	22(62.9)
Age — yr			
Median (range)	35(25-63)	52(25-88)	37(25-88)
Subgroup — no. (%)			
0-15 yr	0	0	0
16–44 yr	20(80)	4(40)	24(68.6)
45-64 yr	5(20)	5(50)	10(28.6)
≥65 yr	0	1(10)	1(2.9)
Underlying Illness — no. (%)			
Hypertension	(12) 3	1(10)	4(11.4)
Coronary heart disease	0	1(10)	1(2.9)
Diabetes	1(4)	1(10)	2(5.7)
Asthma	2(8)	0	2(5.7)
Exposure History — no. (%)			
Huanan seafood wholesale market	0	0	0
Confirmed patients	7(28)	0	7(20)
Confirmed HCWs	3(12)	10(100)	13(37.1)
Gala and Meeting	4(16)	0	4(11.4)
Suspected patients	3(12)	0	3(8.6)
Unknown origins	8(32)	0	8(22.9)
Epidemiological data			
Incubation period— day	N*=4	N=10	N=14
Median(range)	4(1-4)	3(2-12)	3(1-12)
Interquartile range	1.75-4	2-9.5	2-5.25
Interval from the date of onset to the first medical visit— day	N=25	N=10	N=35
Median(range)	2(0-8)	4(0-13)	2(0-13)
Interquartile range	1-3.5	2-7	1-4
Interval from the date of onset to hospital admission— day	N=23	N=4	N=27
Median(range)	5(3-16)	11(4-16)	5(3-16)
Interquartile range	3-7	4.75-15.75	3-10
Serial Interval— day	N=6	N=10	N=16
Median(range)	4(3-7)	3(2-12)	4(2-12)
Interquartile range	3.75-5.5	2-10.25	3-8.5
Management — no. (%)			
Hospitalization	23(92)	4(40)	27(77.1)
Home quarantine	2(8)	6(60)	8(22.9)
Clinical outcome of Feb 12,2020 — no. (%)			
Clinical amelioration remained in hospital	4(16)	2(20)	6(17.1)

Recovered and discharged from hospital	19(76)	2(20)	21(60)
Home quarantine recovered	2(8)	6(60)	8(22.9)
Length of stay in hospital — day			
Median(range)	21(15-28)	13(13-13)	21(13-28)
Interquartile range	17-25		16.5-24.5
Virus shedding — no. (%)			
Virus shedding negative	20(80)		20(57.1)
Virus shedding time — day			
Median(range)	18.5(12-25)		18.5(12-25)
Interquartile range	14.25-21.75		14.25-21.75

*N represents the number of included patients.

Figure Legends

Figure 1 Transmission patterns

Figure 1A Timeline of onset of illness of 37 laboratory-confirmed and two suspected COVID-19 cases, including two laboratory-confirmed index patients admitted to the Department of Neurosurgery, 25 laboratory-confirmed health care workers (HCWs), 12 of whom were in the Department of Neurosurgery, ten of their family members with COVID-19 and two HCWs highly suspected to have infections.

Figure 1B Transmission map of two laboratory-confirmed index patients, 25 laboratory-confirmed HCWs, ten of their family members with COVID-19 and 2 suspected HCWs.

The letters in the Figure represent the patients' IDs. Lines represent direct contacts, dotted lines are suspected contacts. The circle with dashed edges is HCWs with highly suspected infections from the Department of Neurosurgery.

In the Department of Neurosurgery two gatherings were held, a department gala and a meeting among senior nurses on Jan 12 and Jan 13,2020, respectively.

There are nine clear transmission chains. Cluster1: The first hospitalized man (index patient A) in the Department of Neurosurgery with two nurses (C, H) who took care of him. Cluster2: Index patient B at the same ward with A, three nurses (M, Q, O) had close contact with patient B. Nurse O, a probable case had a negative viral nucleic acid test but had COVID-19-like symptoms and imaging findings. Cluster 3: Nurse U with her mother in law f, her mother i and grandmother j. Cluster 4: Nurse P with her husband c. Cluster 5: Nurse F with her husband g and colleague (doctor S)

who had close contact with F at the gala. Cluster 6: Nurse R with her husband e. Cluster 7: Nurse A with her husband a and daughter b. Cluster 8: Nurse B with her boyfriend d. They had contact since Jan 15. Cluster 9: Doctor X with her mother h and father k who is a retired doctor.

There are seven sporadic laboratory confirmed cases. Doctor D who was mainly responsible for gastroscopy, Nurse G in the Department of Cardiology and Nurse I in the Department of Cardiac Surgery, Nurse V in the Laboratory Department who is responsible for delivering clinical specimen the daily, Staff L in the Finance Department. Doctor T is the director of a fever clinic, and Doctor Y is in the Department of Neurology.

Figure 2 Typical statistical probability distribution.

Figure 2A The estimated incubation period distribution

A log-normal distribution was used to fit the incubation period of the case and the probability distribution of the incubation period was estimated according to the information of 14 persons who were confirmed COVID-19 cases and had clear date of exposure and onset.

Figure 2B The estimated serial interval

The probability distribution of the interval time is estimated by using the gamma distribution through nine transmission chains. (i.e., the time interval from onset of illness in one primary case to the onset of illness in the close contact case in a transmission chain)

Figure 2C The estimated distributions of times from illness onset to first medical visit

The Weibull distribution was used to fit and estimate onset-to-first-medical-visit on the dates of the onset of the illness and first medical visit of 35 laboratory confirmed cases and two suspected cases.

Figure 2D The estimated distributions of times from illness onset to hospital admission

The Weibull distribution was used to fit and estimate onset-to-admission distributions on the dates of the onset of the illness and hospital admission of 27 hospitalized patients.

Figure 3 Chest radiographs and computed tomography (CT) of two HCWs

CT images from two HCWs' (A, C) of moderate typical pneumonia.

Figure 3A The CT images of patient C showed a lesion in the posterior segment of left lobe superior lobe. Early on, the range of lesions gradually expanded, from a light GGO to mixed with consolidation and at last, the lesions were significantly reduced 17 days after onset of illness, leaving only a thin GGO under the pleura on Jan 31, 22 days after onset of illness.

Figure 3B The CT images of patient A showed pneumonia in both lower lungs, of which the lower right lung was prominent, and the condition gradually worsened from Jan 7 to 16, but on Jan 22, 17 days after onset of illness GGO became alleviated and resolved significantly on Jan 26, 21 days after onset of illness.

Figure 4 Sequencing Analysis of the Sequences of 12 COVID-19 cases

Figure 4A Full-genome structure and mutation information compared with Wuhan-Hu-1(GenBank accession number, NC_0455122).

WHUHnCoV001-WHUHnCoV008, WHUHnCoV011, WHUHnCoV012, WHUHnCoV0020, and WHUHnCoV021 are sample IDs. The letters following them represent the corresponding patient's IDs in Figure 1B.

Figure 4A Nucleotide differences (vertical colored bars) in the 12 full-genome sequences of SARS-CoV-2 obtained from our cases. Green indicates a synonymous SNV in the query sequence, red a nonsynonymous SNV.

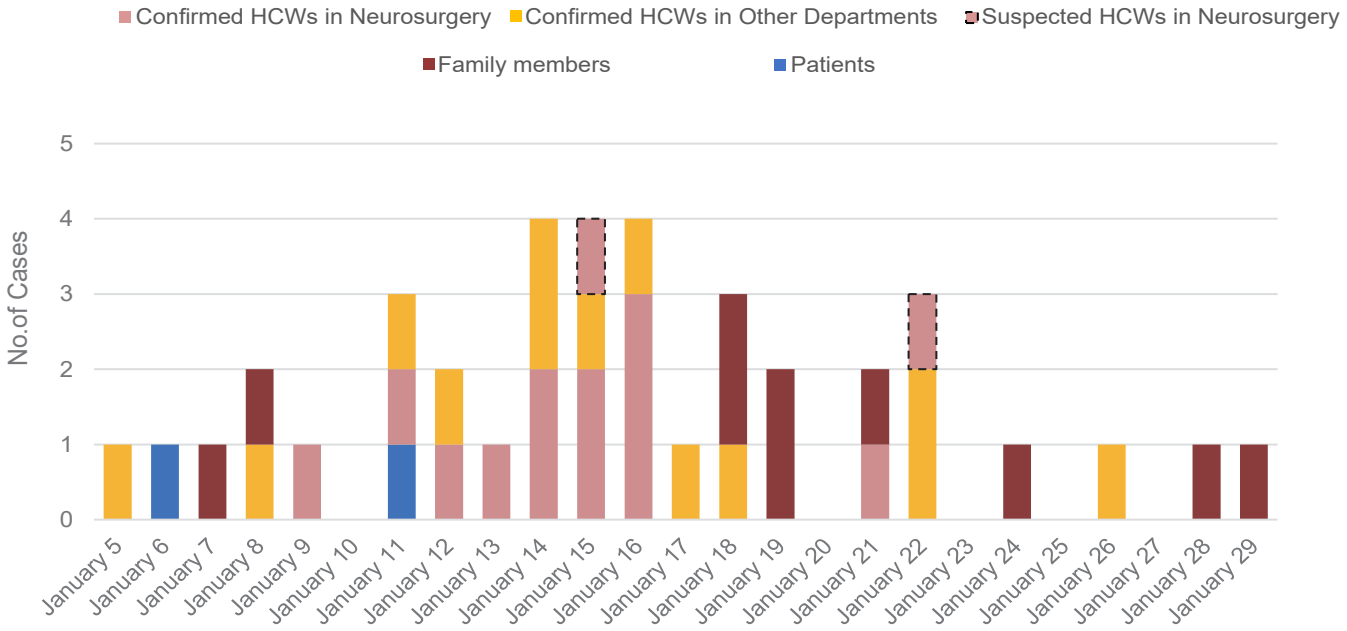
Figure 4B Phylogenetic tree of full-length genomes of SARS-CoV-2 from our 12 samples

Sequences from six HCWs (C, H, J, M, Q, R) in the Department of Neurosurgery and one family members e were closely related in the phylogenetic tree. The obviously separate clade was from HCW B in the Department of Gynecology.

Figure 4C Mutations in Spike protein of WHUHnCoV001.

The reference Spike proteins were from SARS coronavirus isolate Tor2/FP1-10851 (JX163927.1), bat-SL-CoVZC45 (MG772933.1) and Wuhan-Hu-1(NC_045512.2). Compared with bat-SL-CoVZC45 and SARS coronavirus isolate Tor2/FP1-10851, SARS-CoV-2 had four insertion regions (257^{th}-261^{th}, 449^{th}-454^{th}, 479^{th}-495^{th}, 685^{th}-690^{th} site) and three insertion regions (74^{th}-85^{th}, 252^{th} -259^{th}, 685^{th}-690^{th} site) respectively.

A


Confirmed HCWs in Neurosurgery
Confirmed HCWs in Other Departments
Suspected HCWs in Neurosurgery
Family members
Patients
No.of Cases
0
1
2
3
4
5
January 5
January 6
January 7
January 8
January 9
January 10
January 11
January 12
January 13
January 14
January 15
January 16
January 17
January 18
January 19
January 20
January 21
January 22
January 23
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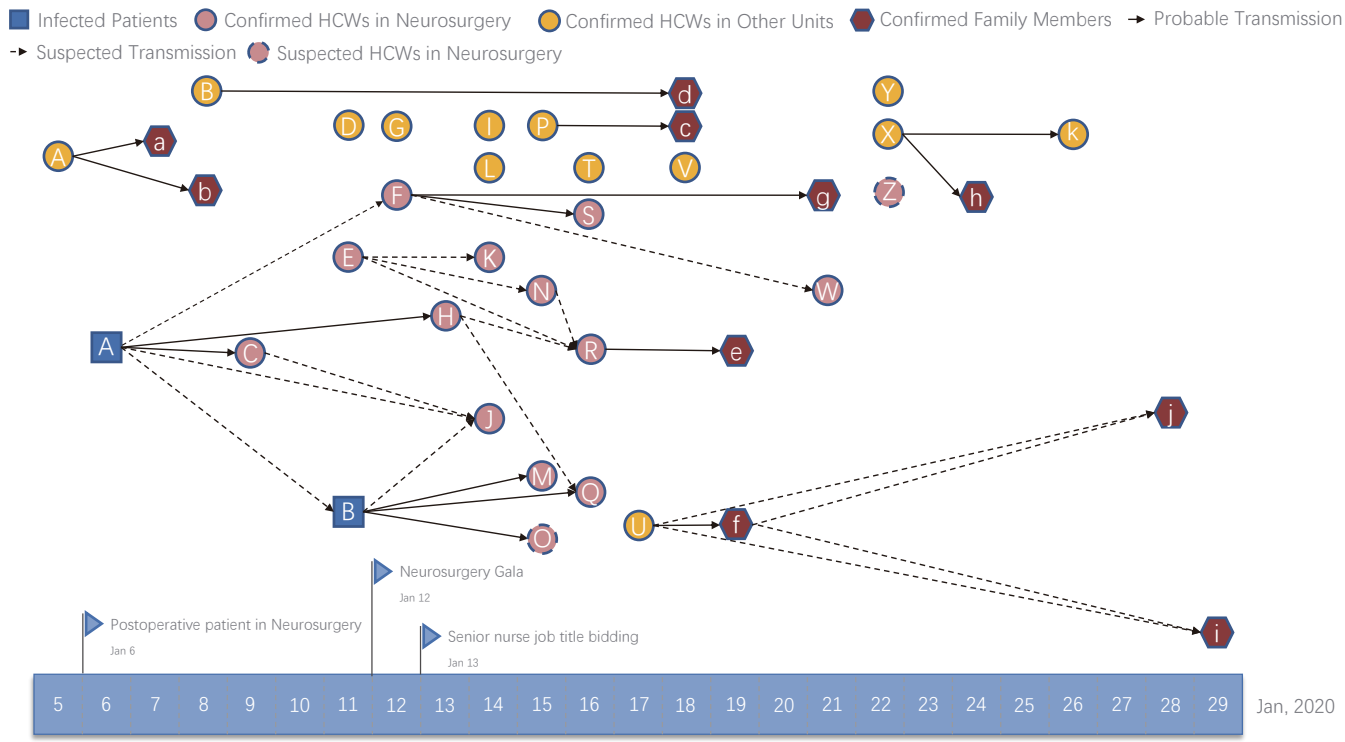
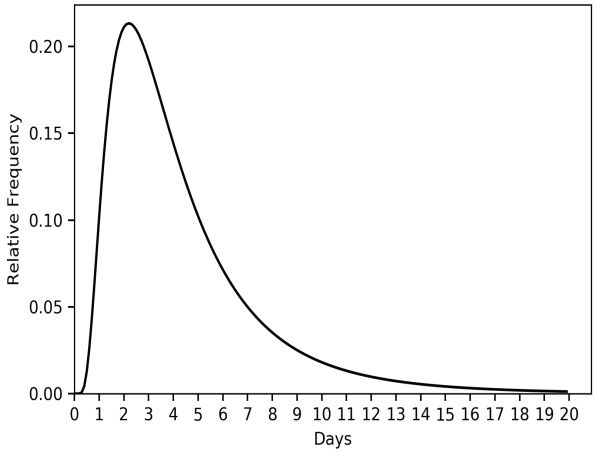
January 26
January 27
January 28
January 29

B


Infected Patients
Confirmed HCWs in Neurosurgery
Confirmed HCWs in Other Units
Confirmed Family Members
Probable Transmission
Suspected Transmission
Suspected HCWs in Neurosurgery
Neurosurgery Gala
Jan 12
Postoperative patient in Neurosurgery
Jan 6
Senior nurse job title bidding
Jan 13
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Jan, 2020

A



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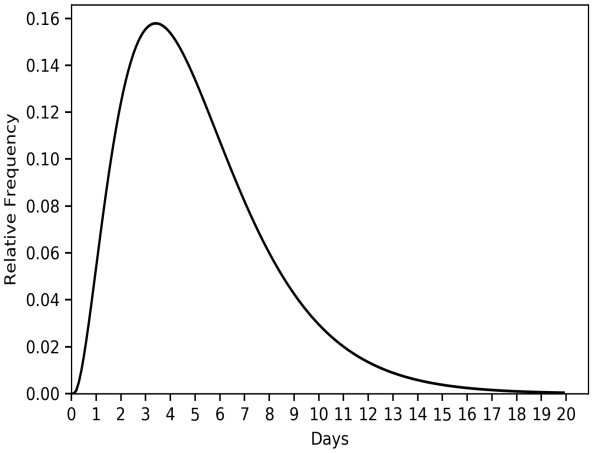
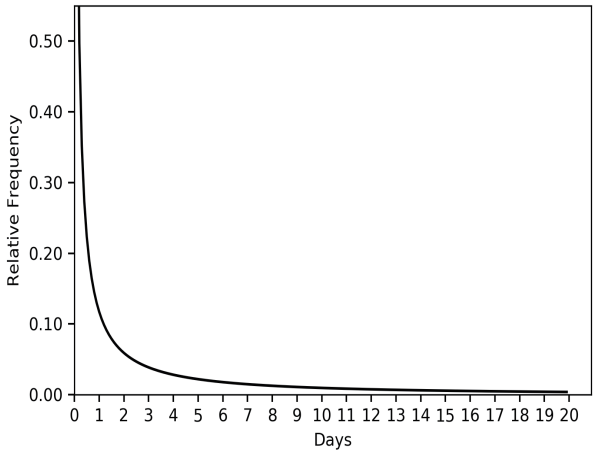


The estimated serial interval

C



The estimated distributions of times from illness onset to first medical visit

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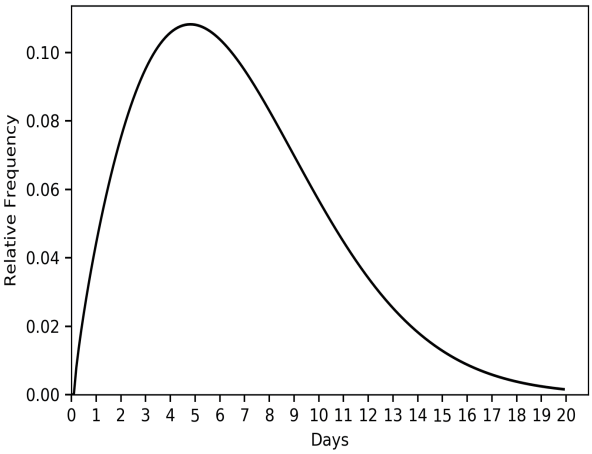
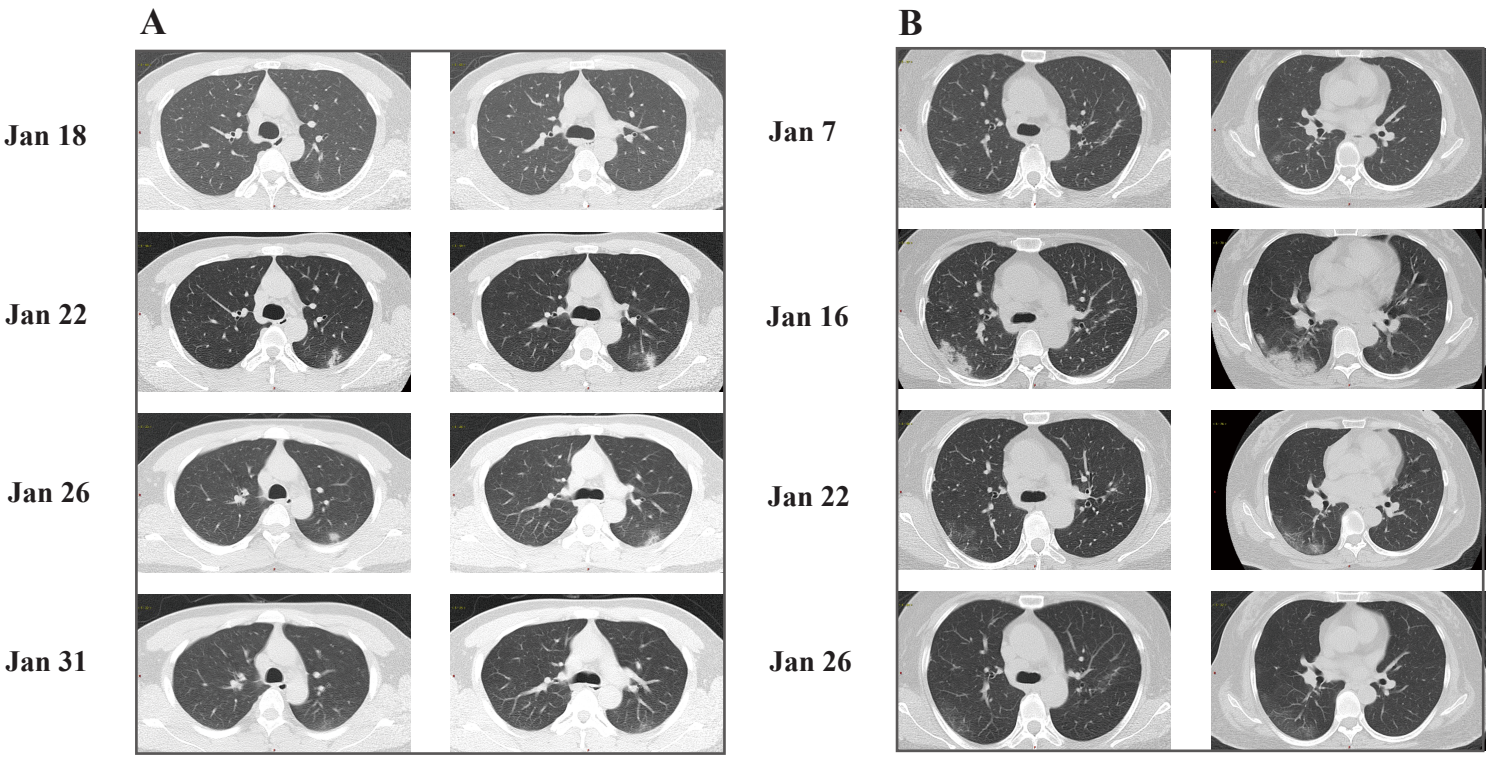


The estimated distributions of times from illness onset to hospital admission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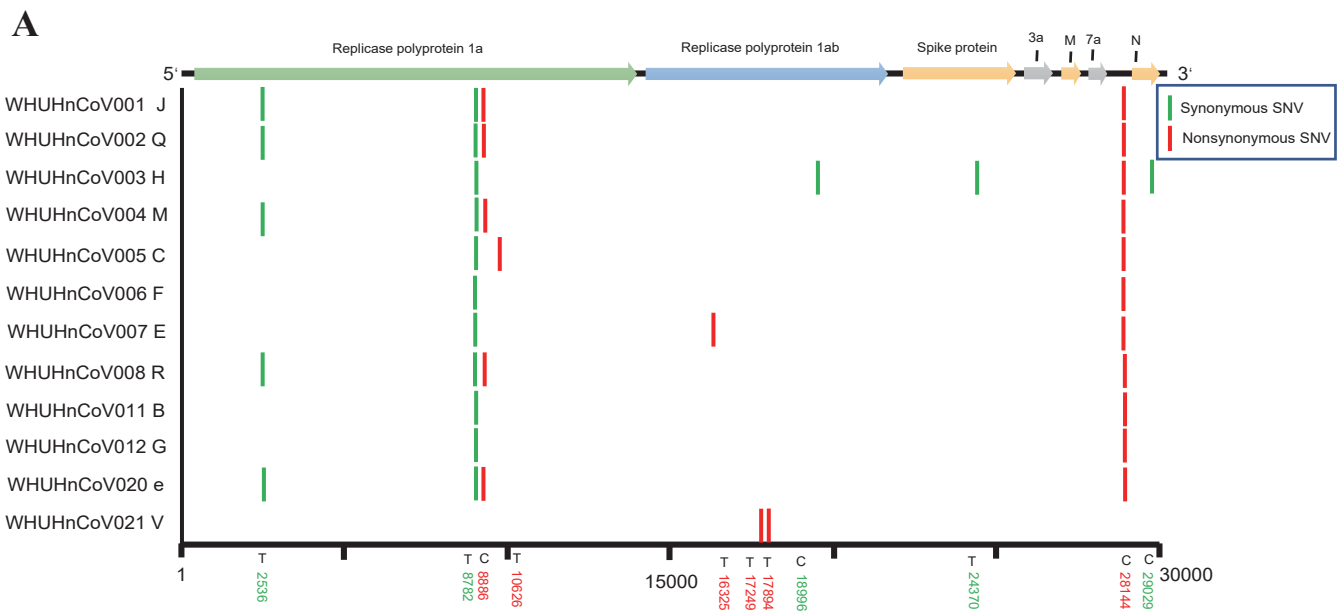
Jan 22
Jan 26
Jan 31
B
Jan 7
Jan 16
Jan 22
Jan 26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Replicase polyprotein 1ab
Spike protein
3a
M
7a
N
5'
3'
Synonymous SNV
Nonsynonymous SNV
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WHUHnCoV002 Q
WHUHnCoV003 H
WHUHnCoV004 M
WHUHnCoV005 C
WHUHnCoV006 F
WHUHnCoV007 E
WHUHnCoV008 R
WHUHnCoV011 B
WHUHnCoV012 G
WHUHnCoV020 e
WHUHnCoV021 V
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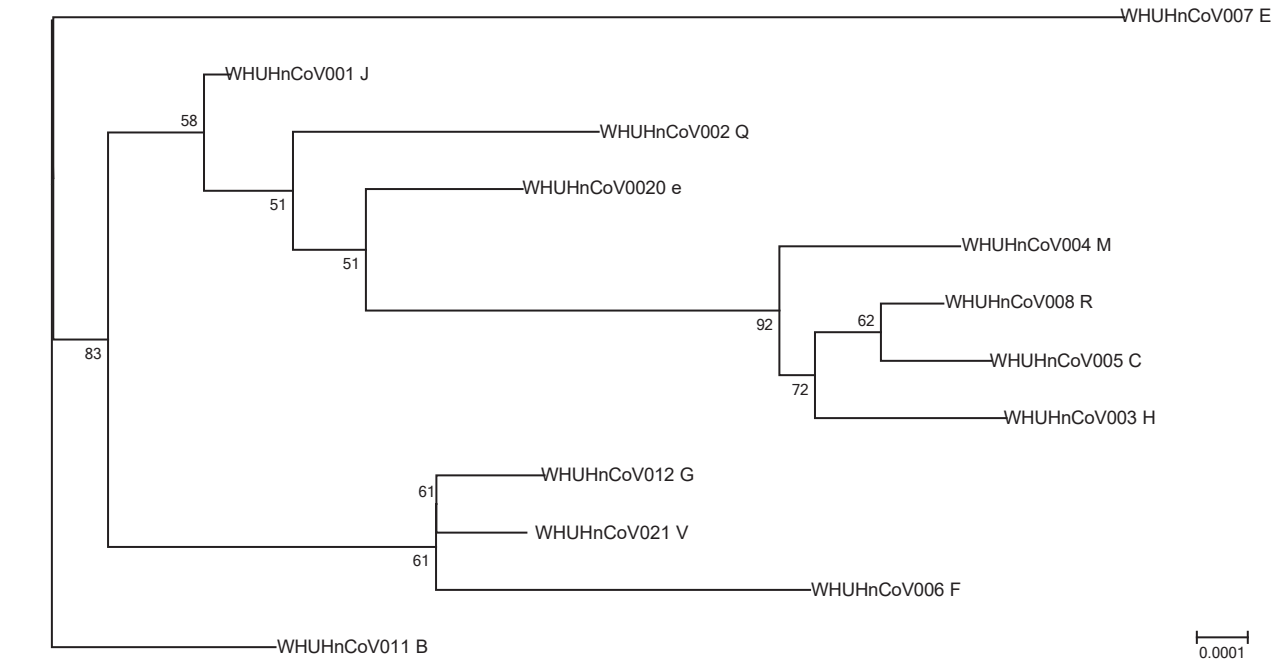
B
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WHUHnCoV001 J
WHUHnCoV002 Q
WHUHnCoV0020 e
WHUHnCoV004 M
WHUHnCoV008 R
WHUHnCoV005 C
WHUHnCoV003 H
WHUHnCoV012 G
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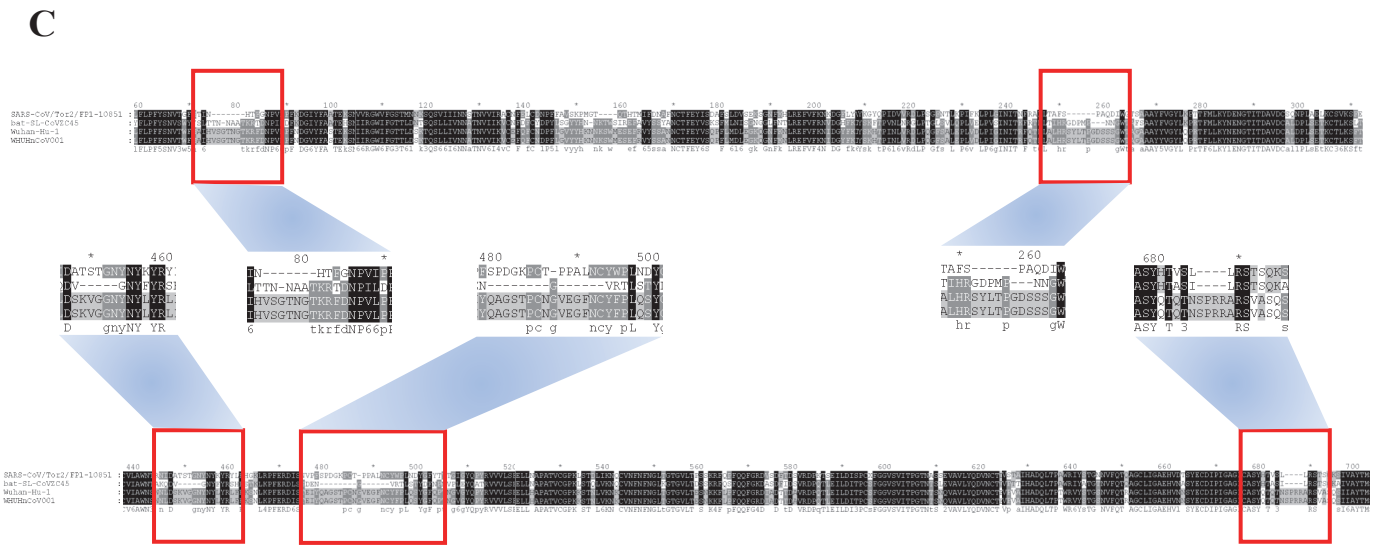
C

Nosocomial Outbreak of 2019 Novel Coronavirus Pneumonia in Wuhan, China

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Running title: Nosocomial Outbreak of Novel Coronavirus Pneumonia

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Contents of Supplements

Supplement 1 Detailed information of exposure history, the symptoms at onset of illness of 9 transmission chains and other sporadic cases as showed in figure 1A and 1B

We found two clusters in the Department of Neurosurgery.

Cluster 1: The first hospitalized man (index patient A) in the Department of Neurosurgery had a fever on the Jan 6, 2020. He was diagnosed as laboratory-confirmed COVID-19 on Jan 16 by Wuhan Center for Disease Control & Prevention. Nurse C who took care of him felt slight malaise on Jan 9, and developed slight dry cough two days later, but his chest roentgenography showed no abnormalities, and was confirmed as COVID-19 on Jan 18 until RT-PCR assays to test for the 2019-nCov be available in hospital then. He was found to be co-infected with A/H1N1 influenza virus after admission. Nurse H took care of the patient A between Jan 9 and Jan 11, she developed symptoms on Jan 13, and was diagnosed on Jan 18. Nurse F was likely to contact with the patient under certain conditions.

Cluster 2: The second patient (index patient B) was admitted to the hospital on Jan 7. Nurse M, Q, O all had close contact with patient, which could be the reason of their infections with 2019-nCoV. Two confirmed patients with five HCWs in close contact with them, acting as a source of infection, spread the virus among the colleagues in the department through daily work and gathering activities. Nurse E wasn't exposed to them but went to a fever clinic without a mask on about Jan 8. At last, 12 HCWs in Department of Neurosurgery were laboratory confirmed COVID-19 cases. Nurse O as probable case had negative viral nucleic acid tests but had COVID-19-like symptoms and imaging findings (Figure S5). And another doctor Z as probable case presented the similar clinical manifestation except for negative viral assay. By far, expect Nurse F, all HCWs in Department of Neurosurgery were recovered and discharged.

We found seven family clusters among HCWs.

Cluster 3: Nurse U developed symptoms on Jan 17 with nasal congestion and rhinorrhea. She lives with her husband and her parents in law, and her parents are in another building but in the same neighborhood. They ate dinner together every night. Then her mother in law f and her mother i and grandmother j developed symptoms successively on Jan 19, Jan 28 and Jan 29, separately.

Cluster 4: Nurse P in Department of Neurology had no clear exposure to any relative patients, but she expressed symptoms of fever on the night of Jan 15, her husband c had fever successively on Jan 18.

Cluster 5: Nurse F developed mild symptoms on Jan 12, but she didn't pay much attention to it and attended Neurosurgery department gala. She lives in the same room with her husband g, her son is in another. Her husband developed symptoms on Jan 21, but her son was fine. Her colleague (doctor S) who had close contact with her on the gala developed symptoms on Jan 16 as well. She suffered severe diarrhea during hospitalization. Even the nucleic acid test of nasopharynx swabs has turned negative and lung CT images got better, the nucleic acid test of stool is still positive one month after onset.

Cluster 6: Nurse R developed symptom of sore throat on Jan 16, later her husband e developed symptoms on Jan 19 immediately.

Cluster 7: Nurse A who treated a child with infectious disease developed symptoms on Jan 5, her husband a and daughter b developed symptoms on Jan 7 and Jan 8. Both of them didn't take much attention until her husband's symptoms worsened with fever and chest tightness on Jan 13. Nurse A was diagnosed on Jan 18 with typical imaging findings of 2019-nCoV pneumonia.

Cluster 8: Nurse B developed symptoms of sore throat, nasal congestion, and intermittent low fever since Jan 8. She met her boyfriend d on Jan 15. Three days later, her boyfriend had headache, later was

diagnosed with 2019-nCoV infection.

Cluster 9: Doctor X was neurological physician who had no clear exposure history. She only had mild symptoms of the upper respiratory tract, and the CT images has no typical infection during hospitalization. Her mother h had cough and fever on Jan 24. Her father k developed myalgia and fever on Jan 26, they went to the hospital and were confirmed with 2019-nCoV infection. Doctor X was confirmed last.

Regarding to HCWs with COVID-19 in other departments in the same hospital, Doctor D who was mainly responsible for gastroscopy fell ill on Jan 11 and did not wear a mask at work. Nurse G in Department of Cardiology and Nurse I in Department of Cardiac Surgery had no clear exposure history but developed symptoms on Jan 12 and 14, 2020, respectively. Staff L in Finance Department had fever on Jan 14, 2020. Doctor T as the director of fever clinic was infected since exposing to many COVID-19 frequently. Nurse V in Department of Laboratory is responsible for the daily delivery clinical specimen of both inpatients and outpatients. Doctor Y in Department of Neurology get fever on Jan 22, who has been exposed to confirmed cases on Jan 19 and Jan 20, 2020.

Supplement 2 Difference between active consultation vs not-active consultation

We compare the difference of clinical symptoms between patients who seek medical treatment actively and those who passively went to see the doctor. We found that mild symptoms are most likely to be ignored, such as nasal congestion and rhinorrhea, which could lead to further spread of the virus. In contrast, symptoms such as fever and poor appetite are more likely to attract people's attention.

Supplement 3 Details of isolation measures

14 HCWs didn't have family members infected. Most of them wearing a mask came home or lived alone in a room. But among the 7(A, B, F, P, R, U, X) family clusters, the HCWs did not pay much attention at the early stage of illness and conduct self-isolation in time. Through investigation, we found that these families were not exposed to other suspected cases. Thus, there is a clear evidence of the transmission between the HCWs and their family members. So timely and effective isolation measures in the early stage of onset may greatly reduce the risk of disease transmission. In contrast, any kind of aggregation activities can greatly increase the likelihood of disease spreading.

Supplementary 4 RNA extraction and real-time RT-PCR assay

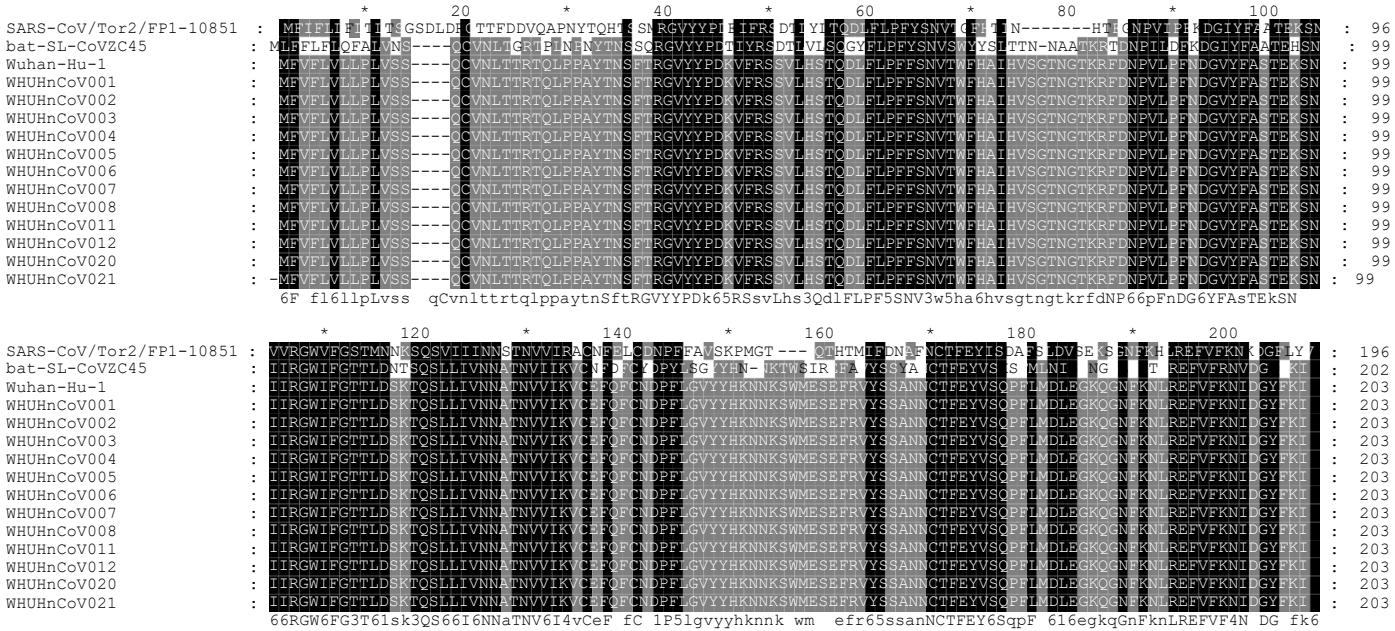
Total RNA was extracted from nasopharynx swabs samples of patients suspected of having 2019-nCoV infection within 2 hours using the respiratory sample RNA isolation kit. In brief, 40 μL of cell lysates were transferred into a collection tube followed by vortex for 10 seconds. After standing at room temperature for 10 minutes, the collection tube was centrifugated at 1000rpm/min for 5minutes. The suspension was used for real-time RT-PCR assay of 2019-nCoV RNA. Two target genes, including open reading frame1ab (ORF1ab) and nucleocapsid protein(N), were simultaneously amplified and tested during the real-time RT-PCR assay. Target 1 (ORF1ab): forward primer CCCTGTGGGTTTTACACTTAA; reverse primer ACGATTGTGCATCAGCTGA. Target2 (N): forward primer GGGGAACTTCTCC TGCTAGAAT; reverse primer CAGACATTTTGCTCTCAAGCTG. RT-PCR assay was performed under the following conditions: incubation at 50 °C for 15 minutes and 95 °C for 2 minutes, 45 cycles of denaturation at 95°C for 3

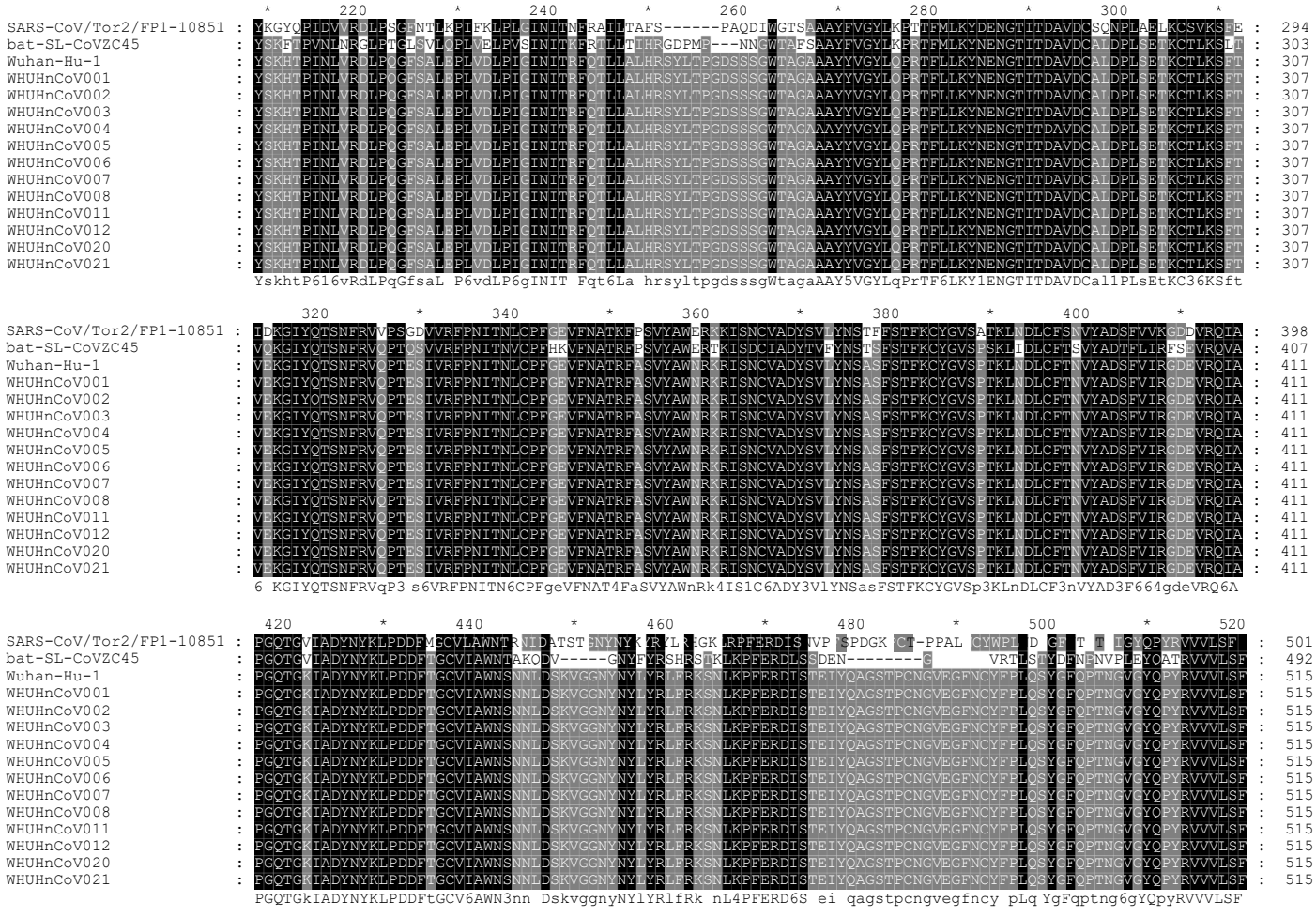
seconds, then annealing, extending and collecting fluorescence signal at 55 °C for 30 seconds[1]. A cycle threshold value (Ct-value) less than 37was defined as a positive test result, and a Ct-value of 40 or more was defined as a negative test. These diagnostic criteria were based on the recommendation by the National Institute for Viral Disease Control and Prevention (China)[2]. A medium load, defined as a Ct-value of 37 to less than 40, required confirmation by retesting.

Supplementary Figures

Figure S1 Comparison of amino acid sequence of Spike protein between 2019-nCoV from our 12 samples, Wuhan-Hu-1 (NC_045512.2), bat-SL-CoVZC45 (MG772933.1) and SARS coronavirus isolate Tor2/FP1-10851 (JX163927.1)

There is no obvious difference between different 2019-nCoVs. Compared with bat-SL-CoVZC45 and SARS coronavirus isolate Tor2/FP1-10851, 2019-nCoV has 4 insertion regions (257th-261th, 449th-454th, 479th-495th, 685th-690th site) and 3 insertion regions (74th-85th, 252th -259th, 685th-690th site) respectively.

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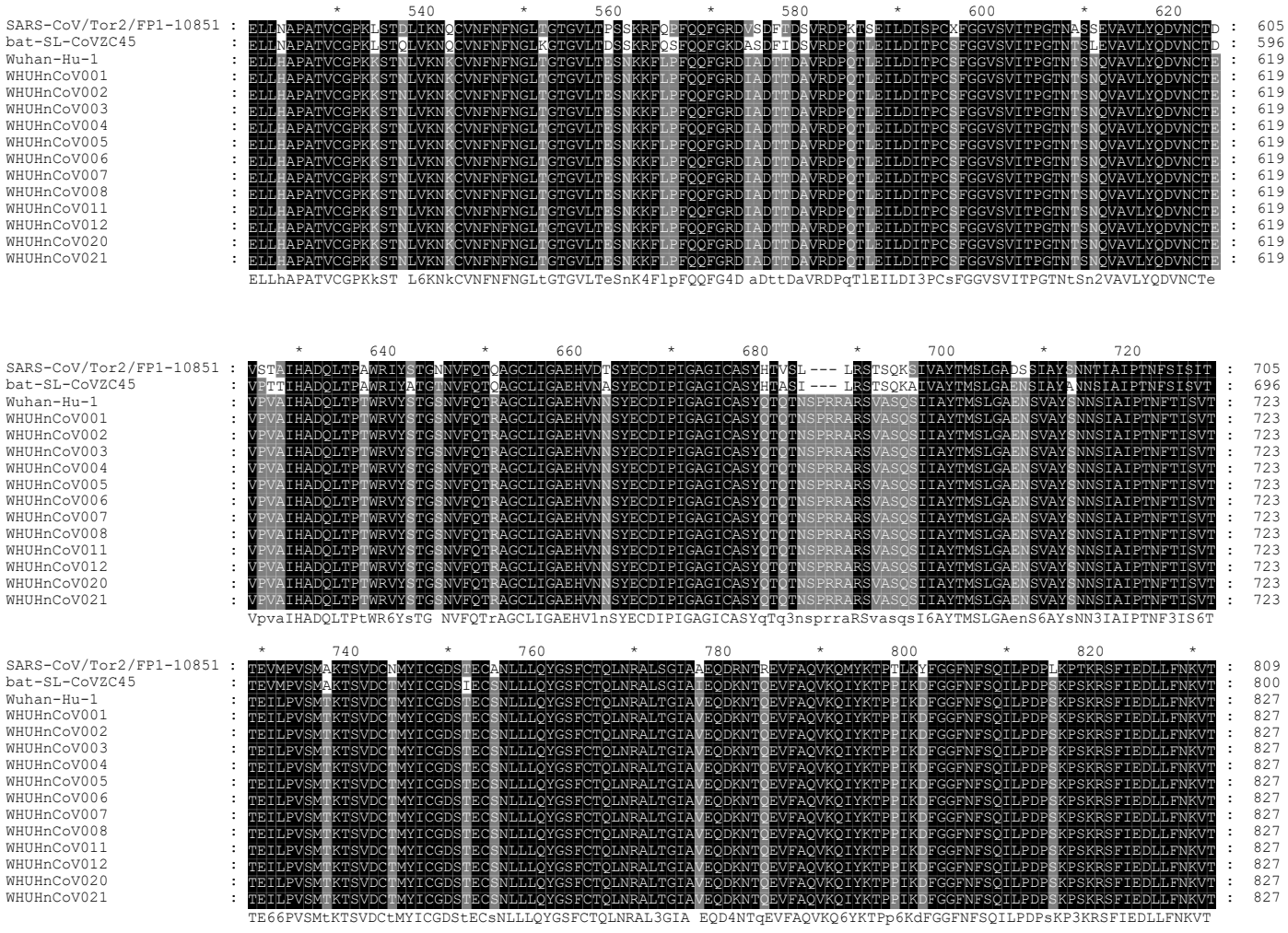
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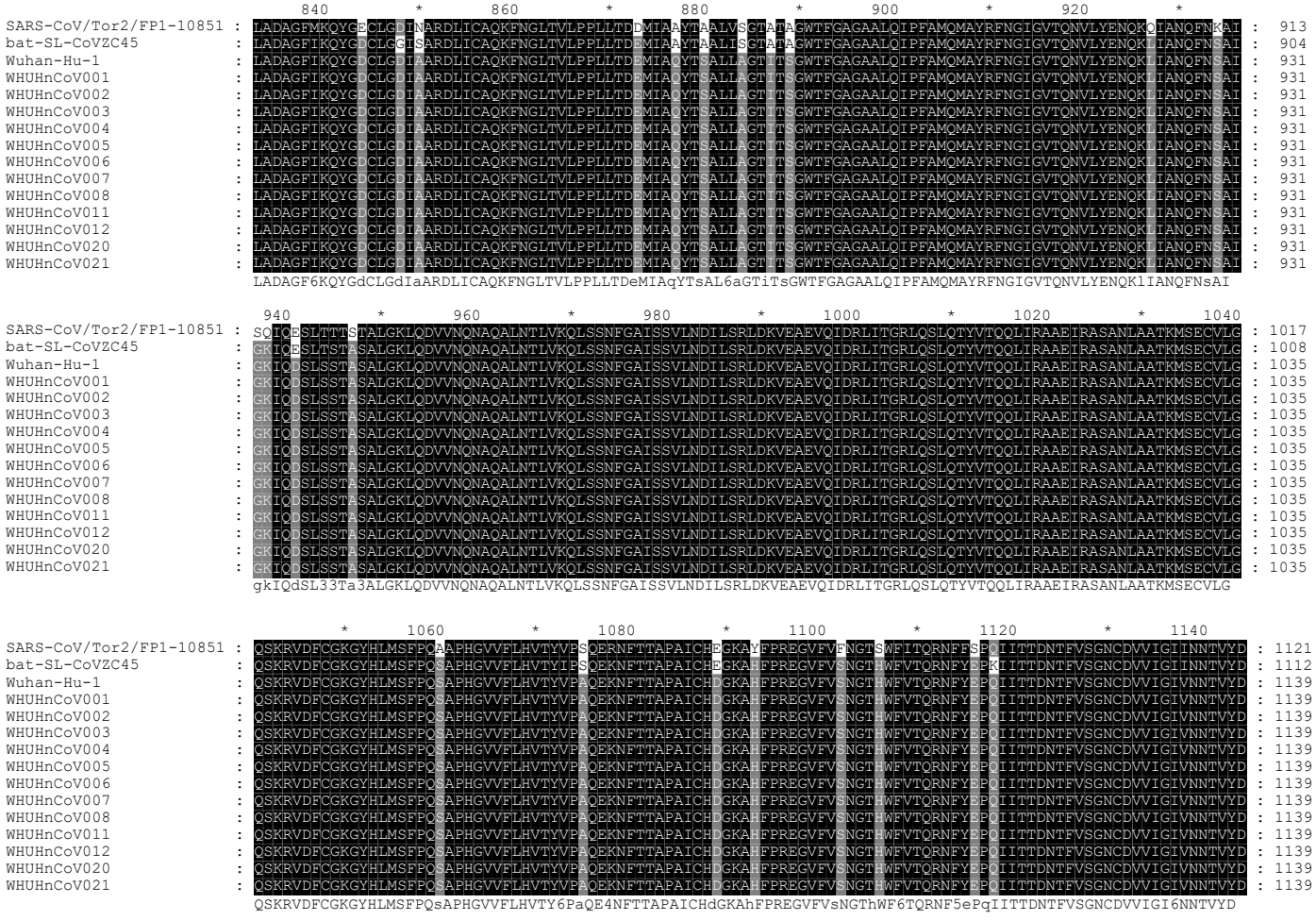
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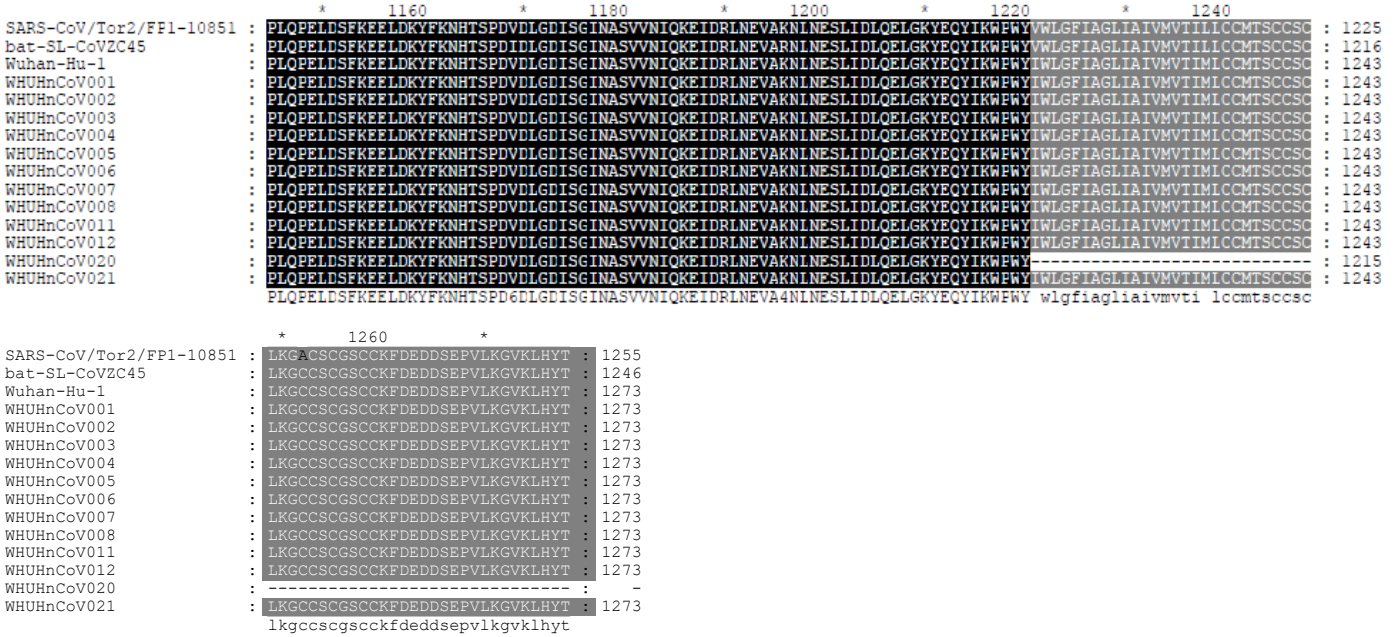
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bat-SL-CoVZC45 : LKGCCSCGSCCKFDEDDSEPVLKGVKLHYT : 1246
Wuhan-Hu-1 : LKGCCSCGSCCKFDEDDSEPVLKGVKLHYT : 1273
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WHUHnCoV020 : ---------------------------- : -
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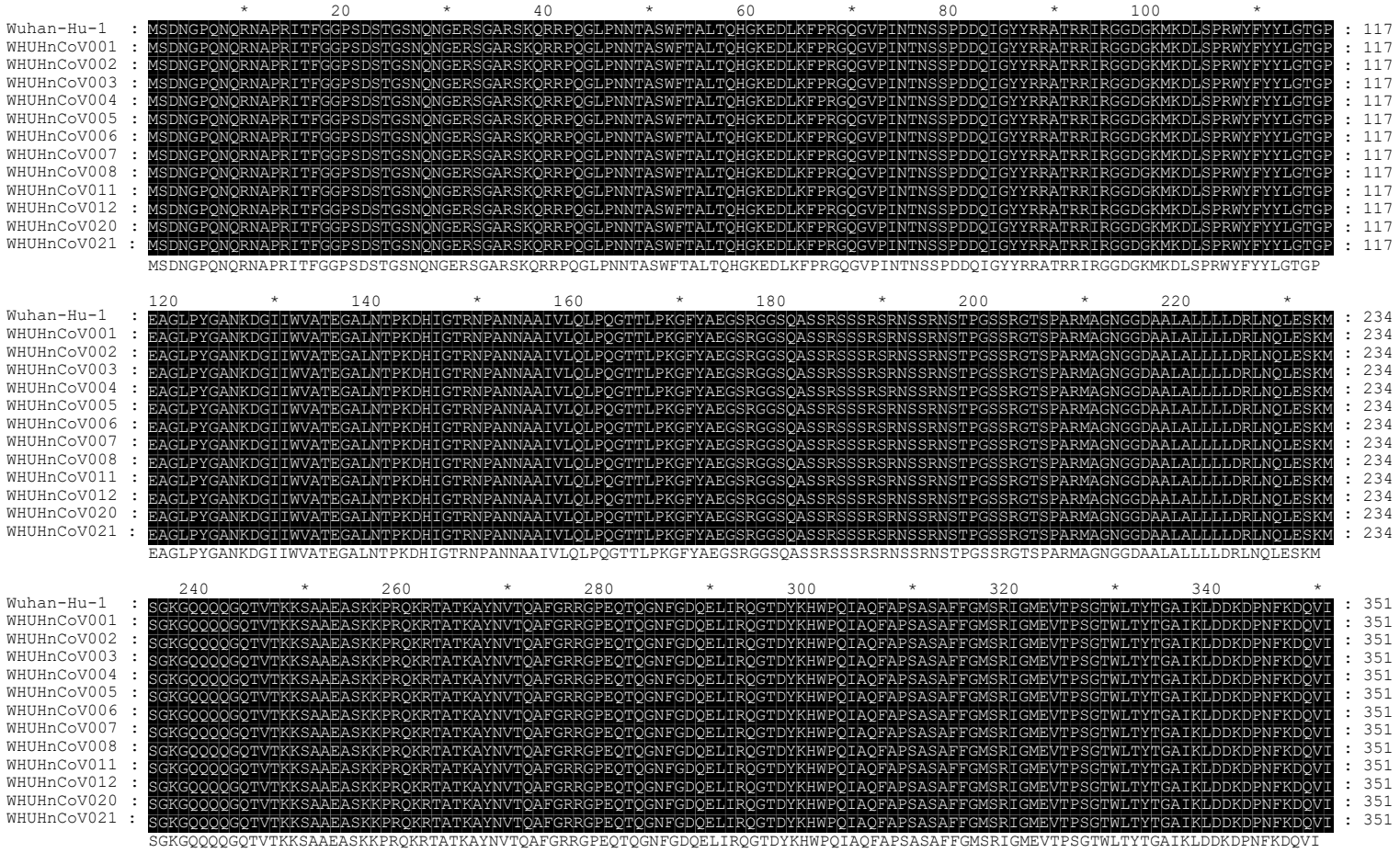
Figure S2 Comparison of amino acid sequence of N protein between 2019-nCoV from our 12 samples and Wuhan-Hu-1 (NC_045512.2)

The structure of N protein is stable and conserved.



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```

Figure S3 The phylogenetic tree of full-genome of 2019-nCoV from our 12 samples,10 previously identified 2019-nCoV and other coronavirus

The phylogenetic tree was aligned with the use of FFT-NS-2 model. Maximum-likelihood phylogenies were inferred under a generalized-time-reversal (GTR)+ Gamma substitution model and bootstrapped 1000 times to assess confidence. 2019-nCoVs form a monophyletic clade with a bootstrap support of 100%. The most closely related sequence to this clade is bat-SL-CoV.

Figure S4 The phylogenetic tree of Spike protein between 2019-nCoV from our 12 samples,10 previously identified 2019-nCoV and other coronavirus

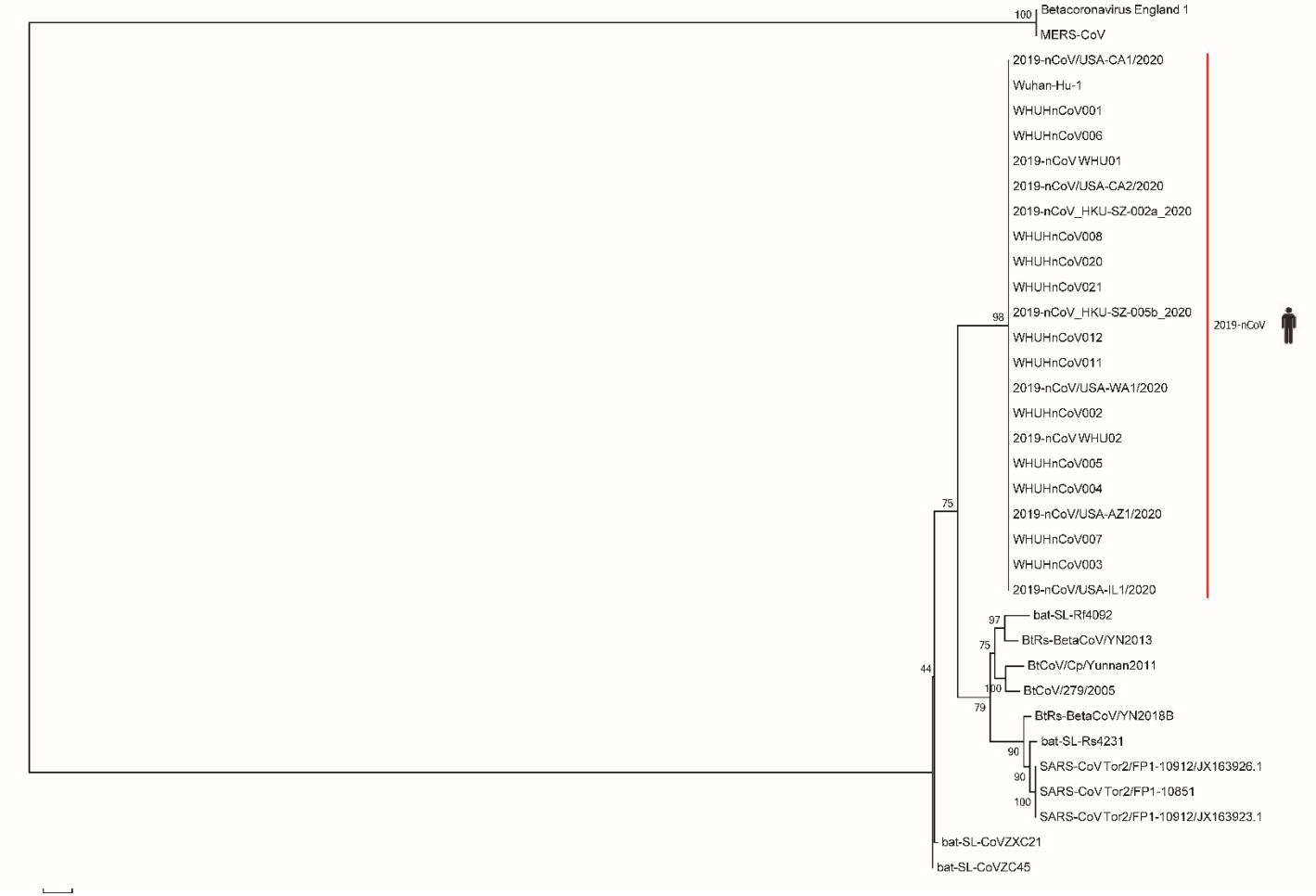
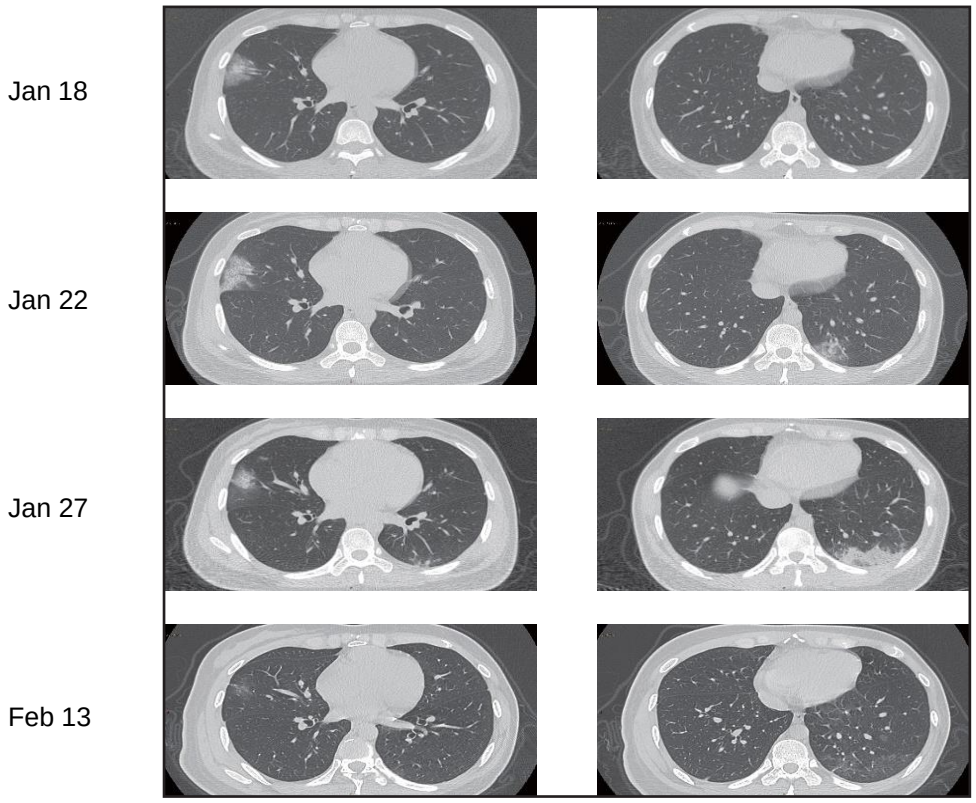


Figure S5 Chest radiographs and computed tomography (CT) of HCW O

Nurse O who was a highly suspected case had negative viral nucleic acid tests but had COVID-19-like symptoms and imaging findings. There is a flaky GGO under the pleura in the middle lobe of right lung on Jan 18, 2020. The density of lesion increased, and the interlobular septum thickened, showing paving stones sign as well as interpleural pleura traction, and a GGO appear in the posterior basal segment of the left lung on Jan 22, 2020. The range and the density of lesions in the right middle lobe reduced, and the lesion in the posterior basal and outer basal segments of the lower lobe of the left lung is enlarged and the density increased on Jan 27, 2020. Most of the lesions disappeared, leaving a few GGO and fiber cable shadows on Feb 13, 2020, 29 days after the onset of illness. The infiltrated can be waning.



Supplementary Tables

Table S1 Clinical Characteristics and Treatments in Patients with Laboratory-Confirmed Novel Coronavirus Pneumonia

Variable	Value
Signs and symptoms on admission	N*=35
Fever	
Any — no. (%)	30(85.7)
Maximal temperature — °C	38.8±1.4
37.3–38.0°C	7(23.3)
38.1–39.0°C	12(40)
>39.0°C	4(13.3)
N/A	7(23.3)
Cough — no. (%)	19(54.3)
Chest tightness — no. (%)	14(40)
Myalgia — no. (%)	16(45.7)
Malaise — no. (%)	26(74.3)
Headache — no. (%)	13(37.1)
Sore throat — no. (%)	17(48.6)
Rhinorrhoea — no. (%)	6(17.1)
Poor appetite — no. (%)	22(62.9)
Nausea and vomiting — no. (%)	3(8.6)
Diarrhoea — no. (%)	9(25.7)
Palpitation — no. (%)	4(11.4)
Chest pain — no. (%)	4(11.4)
Night sweat — no. (%)	1(2.9)
Rash — no. (%)	1(2.9)
Hypoxemia — no. (%)	3(8.6)
Treatment— no. (%)	
Glucocorticoids	0
Oxygen therapy	6(17.1%)

*N represents the number of included patients.

Table S2 Laboratory results of Patients with Laboratory-Confirmed Novel Coronavirus Pneumonia

Characteristic	Value
Laboratory exams on admission	
Blood routine	N*=31
WBC count (G/L)	
Median	4.5
Interquartile range	4.12-6.34
Subgroup — no. (%)	
<3.5	4(12.9)
3.5-9.5	27(87.1)
>9.5	0
Neutrophil count (G/L)	
Median	2.95
Interquartile range	2.17-4.31
Subgroup — no. (%)	
<1.8	5(16.1)
1.8-6.3	25(80.6)
>6.3	1(3.2)
Lymphocyte count (G/L)	
Median	1.13
Interquartile range	0.815-1.515
Subgroup — no. (%)	
<1.1	13(43.3)
1.1-3.2	17(56.7)
>3.2	0
Hemoglobin (g/L)	
Median	136
Interquartile range	125.5-151
Platelet count (G/L)	
Median	170
Interquartile range	148.5-202.5
Subgroup — no. (%)	
<125	2(6.9)
125-350	27(93.1)
>350	0
Blood biochemistry	N=26
Alanine aminotransferase (U/L)	
Median	18
Interquartile range	13-28.5
Subgroup — no. (%)	
≤ 40	22(84.6)
> 40	4(15.4)
Aspartate aminotransferase (U/L)	

Median	22.5
Interquartile range	19-28
Subgroup — no. (%)	
≤ 40	25(96.2)
> 40	1(3.8)
Albumin (g/L)	
Median	41.6
Interquartile range	38.6-44.125
Total bilirubin (μmol/L)	
Median	8.75
Interquartile range	6.9-10.1
Direct bilirubin(μmol/L)	
Median	3.4
Interquartile range	2.225-4
Creatinine (μmol/L)	
Median	64.65
Interquartile range	55.6-77.85
Subgroup — no. (%)	
≤133	26(100)
> 133	0
Blood urea nitrogen (mmol/L)	
Median	3.76
Interquartile range	2.85-4.23
Creatine kinase (U/L)	
Median	55.5
Interquartile range	45-88.75
Subgroup — no. (%)	
≤174	23(95.8)
> 174	1(4.2)
Lactate dehydrogenase (U/L)	
Median	187
Interquartile range	165-262
Subgroup — no. (%)	
≤245	16(69.6)
> 245	7(30.4)
Infection-related biomarkers	N=22
C-reactive protein(mg/L)	
Subgroup — no. (%)	
< 8	11(50)
≥8	11(50)

Procalcitonin (μg/ml)	
Subgroup — no. (%)	
< 0.5	21(95.5)
≥0.5	1(4.5)
Erythrocyte sedimentation rate(mm/h)	
Median	10.5
Interquartile range	6-23.5
Interleukin-6(pg/ml)	
Median	4.68
Interquartile range	3.06-7.17
Chest x-ray and CT findings on admission— no. (%)	
Ground-glass opacity (GGO) dominating	29(82.9)
Consolidation dominating	4(11.4)
GGO and consolidation integrating	1(2.9)
Normal	1(2.9)

*N represents the number of included patients.

Blood routine:

WBC count (G/L) Normal Range: 3.5-9.5

Neutrophil count (G/L) Normal Range: 1.8-6.3

Lymphocyte count (G/L) Normal Range: 1.1-3.2

Hemoglobin (g/L) Normal Range: 130-175

Platelet count (G/L) Normal Range: 125-350

Blood biochemistry:

Alanine aminotransferase (U/L) Normal Range: 5-40

Aspartate aminotransferase (U/L) Normal Range: 8-40

Albumin (g/L) Normal Range: 35-55

Total bilirubin (μmol/L) Normal Range: 5.1-19

Direct bilirubin(μmol/L) Normal Range: 1.7-6.8

Creatinine (μmol/L) Normal Range: 44-133

Blood urea nitrogen (mmol/L) Normal Range: 2.9-8.2

Creatine kinase (U/L) Normal Range: 38-174

Lactate dehydrogenase (U/L) Normal Range: 109-245

Infection-related biomarkers

C-reactive protein(mg/L) Normal Range: < 8

Procalcitonin (μg/ml) Normal Range: < 0.5

Erythrocyte sedimentation rate(mm/h) Normal Range: < 20

Interleukin-6(pg/ml) Normal Range: 0.1-2.9

Table S3 Corresponding sequencing sample ids and patient ids

Sample ID	Patient ID
WHUHnCoV001	J
WHUHnCoV002	Q
WHUHnCoV003	H
WHUHnCoV004	M
WHUHnCoV005	C
WHUHnCoV006	F
WHUHnCoV007	E
WHUHnCoV008	R
WHUHnCoV011	B
WHUHnCoV012	G
WHUHnCoV020	e
WHUHnCoV021	V

Table S4 The detailed mutation information of our 12 samples.

Sample ID	Pos	Ref	Alt
WHUHnCoV001	2536	C	T
WHUHnCoV001	8782	C	T
WHUHnCoV001	8886	T	C
WHUHnCoV001	28144	T	C
WHUHnCoV002	2536	C	T
WHUHnCoV002	8782	C	T
WHUHnCoV002	8886	T	C
WHUHnCoV002	28144	T	C
WHUHnCoV003	8782	C	T
WHUHnCoV003	18996	T	C
WHUHnCoV003	24370	C	T
WHUHnCoV003	28144	T	C
WHUHnCoV003	29029	T	C
WHUHnCoV004	2536	C	T
WHUHnCoV004	8782	C	T
WHUHnCoV004	8886	T	C
WHUHnCoV004	28144	T	C
WHUHnCoV005	8782	C	T
WHUHnCoV005	10626	C	T
WHUHnCoV005	28144	T	C
WHUHnCoV006	8782	C	T
WHUHnCoV006	28144	T	C
WHUHnCoV007	8782	C	T
WHUHnCoV007	16325	G	C
WHUHnCoV007	28144	T	C
WHUHnCoV008	2536	C	T
WHUHnCoV008	8782	C	T
WHUHnCoV008	8886	T	C
WHUHnCoV008	28144	T	C
WHUHnCoV011	8782	C	T
WHUHnCoV011	28144	T	C
WHUHnCoV012	8782	C	T
WHUHnCoV012	28144	T	C
WHUHnCoV020	2536	C	T
WHUHnCoV020	8782	C	T
WHUHnCoV020	8886	T	C
WHUHnCoV020	28144	T	C
WHUHnCoV021	17249	C	T
WHUHnCoV021	17894	C	T

The reference genomes we used was Wuhan-Hu-1 (GenBank accession number, NC_045512.2)

Table S5 The integrated introduction of all 61 published 2019-nCoV

Strain	Gisaid_epi_isl	Genbank_accession	Date	Country	Location	Segment	Host	Originating_lab	Submitting_lab	Authors
2019-nCoV WHU01	EPI_ISL_406716	MN988668	2020/1/2	China	Wuhan	genome	human	State Key Laboratory of Virology, Wuhan University	State Key Laboratory of Virology, Wuhan University	Chen et al
2019-nCoV WHU02	EPI_ISL_406717	MN988669	2020/1/2	China	Wuhan	genome	human	State Key Laboratory of Virology, Wuhan University	State Key Laboratory of Virology, Wuhan University	Chen et al
2019-nCoV/USA-AZ1/2020	EPI_ISL_406223	MN997409	2020/1/22	USA	Phoenix	genome	human	Arizona Department of Health Services, Phoenix, AZ, USA	Pathogen Discovery, Respiratory Viruses Branch, Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA	Tao et al
2019-nCoV/USA-CA1/2020	EPI_ISL_406034	MN994467	2020/1/23	USA	Los Angeles	genome	human	California Department of Public Health, Richmond CA, USA	Pathogen Discovery, Respiratory Viruses Branch, Division of Viral Diseases, Centers for Dieases Control and Prevention, Atlanta GA, USA	Uehara et al
2019-nCoV/USA-CA2/2020	EPI_ISL_40603	MN994468	2020/1/22	USA	Orange	genome	huma	California	Pathogen Discovery,	Uehara

	6				County		n	Department of Public Health, Richmond CA, USA	Respiratory Viruses Branch, Division of Viral Diseases, Centers for Dieases Control and Prevention, Atlanta GA, USA	et al
2019-nCoV/USA-IL1/2020	EPI_ISL_404253	MN988713	2020/1/21	USA	Chicago	genome	human	IL Department of Public Health Chicago Laboratory, Chicago, IL	Pathogen Discovery, Respiratory Viruses Branch, Division of Viral Diseases, Centers for Dieases Control and Prevention, Atlanta, GA	Tao et al
2019-nCoV/USA-WA1/2020	EPI_ISL_404895	MN985325	2020/1/19	USA	Seattle	genome	human	Providence Regional Medical Center	Division of Viral Diseases, Centers for Disease Control and Prevention	Queen et al
2019-nCoV_HKU-SZ-002a_2020	EPI_ISL_406030	MN938384	2020/01/XX	China	Shenzhen	genome	human	University of Hong Kong-Shenzhen Hospital	University of Hong Kong-Shenzhen Hospital	Chan et al
2019-nCoV_HKU-SZ-005b_2020	EPI_ISL_405839	MN975262	2020/01/XX	China	Shenzhen	genome	human	University of Hong Kong-Shenzhen Hospital	University of Hong Kong-Shenzhen Hospital	Chan et al
BetaCoV/Australia/NSW01/2020	EPI_ISL_407893	/	2020/1/24	Australia	Sydney	genome	human	Centre for Infectious Diseases and Microbiology Laboratory	NSW Health Pathology - Institute of Clinical Pathology and Medical Research; Westmead	Eden et al

								Services, Westmead, Australia	Hospital; University of Sydney, Westmead, Australia	
BetaCoV/Australia/VIC01/2020	EPI_ISL_406844	/	2020/1/25	Australia	Clayton	genome	human	Monash Medical Centre, Melbourne, Australia	Collaboration between the University of Melbourne at The Peter Doherty Institute for Infection and Immunity, and the Victorian Infectious Disease Reference Laboratory, Melbourne, Australia	Caly et al
BetaCoV/England/01/2020	EPI_ISL_407071	/	2020/1/29	United Kingdom	England	genome	human	Respiratory Virus Unit, Microbiology Services Colindale, Public Health England, London, United Kingdom	Respiratory Virus Unit, Microbiology Services Colindale, Public Health England, London, United Kingdom	Galiano et al
BetaCoV/England/02/2020	EPI_ISL_407073	/	2020/1/29	United Kingdom	England	genome	human	Respiratory Virus Unit, Microbiology Services Colindale, Public Health England, London, United Kingdom	Respiratory Virus Unit, Microbiology Services Colindale, Public Health England, London, United Kingdom	Galiano et al
BetaCoV/Finland/1/2020	EPI_ISL_407079	MT020781	2020/1/29	Finland	Rovaniemi	genome	human	Lapland Central Hospital, Finland	Department of Virology, University of Helsinki	Smura et al

									and Helsinki University Hospital, Helsinki, Finland	
BetaCoV/Foshan/20SF207/2020	EPI_ISL_406534	/	2020/1/22	China	Foshan	genome	human	Guangdong Provincial Institute of Public Health, Guangzhou, China	Guangdong Provincial Center for Diseases Control and Prevention, Guangzhou, China	Kang et al
BetaCoV/Foshan/20SF210/2020	EPI_ISL_406535	/	2020/1/22	China	Foshan	genome	human	Guangdong Provincial Institute of Public Health, Guangzhou, China	Guangdong Provincial Center for Diseases Control and Prevention, Guangzhou, China	Kang et al
BetaCoV/Foshan/20SF211/2020	EPI_ISL_406536	/	2020/1/22	China	Foshan	genome	human	Guangdong Provincial Institute of Public Health, Guangzhou, China	Guangdong Provincial Center for Diseases Control and Prevention, Guangzhou, China	Kang et al
BetaCoV/France/IDF0372/2020	EPI_ISL_406596	/	2020/1/23	France	Paris	genome	human	Department of Infectious and Tropical Diseases, Bichat Claude Bernard Hospital, Paris, France	National Reference Center for Viruses of Respiratory Infections, Institut Pasteur, Paris, France	Albert et al
BetaCoV/France/IDF0373/2020	EPI_ISL_406597	/	2020/1/23	France	Paris	genome	human	Department of Infectious and Tropical Diseases, Bichat Claude Bernard Hospital,	National Reference Center for Viruses of Respiratory Infections, Institut Pasteur, Paris, France	Albert et al

								Paris, France		
BetaCoV/Germany/BavPat1/2020	EPI_ISL_406862	/	2020/1/28	Germany	Starnberg	genome	human	Charite Universitaetsmedizin Berlin, Institute of Virology; Institut fuer Mikrobiologie der Bundeswehr, Munich, Germany	Charite Universitaetsmedizin Berlin, Institute of Virology, Berlin, Germany	Corman et al
BetaCoV/Guangdong/20SF012/2020	EPI_ISL_403932	/	2020/1/14	China	Shenzhen	genome	human	Guangdong Provincial Center for Diseases Control and Prevention; Guangdong Provinical Public Health, Guangzhou, China	Department of Microbiology, Guangdong Provincial Center for Diseases Control and Prevention; Guangdong Provinical Public Health, Guangzhou, China	Kang et al
BetaCoV/Guangdong/20SF013/2020	EPI_ISL_403933	/	2020/1/15	China	Shenzhen	genome	human	Guangdong Provincial Center for Diseases Control and Prevention; Guangdong Provinical Public Health, Guangzhou, China	Department of Microbiology, Guangdong Provincial Center for Diseases Control and Prevention; Guangdong Provinical Public Health, Guangzhou, China	Kang et al
BetaCoV/Guangdong/20SF014/2020	EPI_ISL_403934	/	2020/1/15	China	Shenzhen	genome	human	Guangdong Provincial Center	Department of Microbiology,	Kang et al

								for Diseases Control and Prevention; Guangdong Provinical Public Health, Guangzhou, China	Guangdong Provincial Center for Diseases Control and Prevention; Guangdong Provinical Public Health, Guangzhou, China	
BetaCoV/Guangdong/20SF025/2020	EPI_ISL_403935	/	2020/1/15	China	Shenzhen	genome	human	Guangdong Provincial Center for Diseases Control and Prevention; Guangdong Provinical Public Health, Guangzhou, China	Department of Microbiology, Guangdong Provincial Center for Diseases Control and Prevention; Guangdong Provinical Public Health, Guangzhou, China	Kang et al
BetaCoV/Guangdong/20SF028/2020	EPI_ISL_403936	/	2020/1/17	China	Zhuhai	genome	human	Guangdong Provincial Center for Diseases Control and Prevention; Guangdong Provinical Public Health, Guangzhou, China	Department of Microbiology, Guangdong Provincial Center for Diseases Control and Prevention; Guangdong Provinical Public Health, Guangzhou, China	Kang et al
BetaCoV/Guangdong/20SF040/2020	EPI_ISL_403937	/	2020/1/18	China	Zhuhai	genome	human	Guangdong Provincial Center for Diseases Control and Prevention;	Department of Microbiology, Guangdong Provincial Center for Diseases	Kang et al

								Guangdong Provinical Public Health, Guangzhou, China	Control and Prevention; Guangdong Provinical Public Health, Guangzhou, China	
BetaCoV/Guangdong/20SF174/2020	EPI_ISL_406531	/	2020/1/22	China	Zhuhai	genome	human	Guangdong Provincial Institute of Public Health, Guangzhou, China	Guangdong Provincial Center for Diseases Control and Prevention, Guangzhou, China	Kang et al
BetaCoV/Guangdong/20SF201/2020	EPI_ISL_406538	/	2020/1/23	China	Guangdong	genome	human	Guangdong Provincial Institute of Public Health, Guangzhou, China	Guangdong Provincial Center for Diseases Control and Prevention, Guangzhou, China	Kang et al
BetaCoV/Guangzhou/20SF206/2020	EPI_ISL_406533	/	2020/1/22	China	Guangzhou	genome	human	Guangdong Provincial Institute of Public Health, Guangzhou, China	Guangdong Provincial Center for Diseases Control and Prevention, Guangzhou, China	Kang et al
BetaCoV/Hangzhou/HZCDC0001/2020	EPI_ISL_407313	/	2020/1/19	China	Hangzhou	genome	human	Hangzhou Center for Disease Control and Prevention	Hangzhou Center for Disease Control and Prevention	/
BetaCoV/Japan/AI/I-004/2020	EPI_ISL_407084	LC521925	2020/1/25	Japan	Aichi	genome	human	Department of Virology III, National Institute of Infectious Diseases, Tokyo, Japan	Pathogen Genomics Center, National Institute of Infectious Diseases, Tokyo, Japan	Sekizuka et al
BetaCoV/Korea/KCDC03/2020	EPI_ISL_407193	/	2020/1/25	South Korea	Gyeonggi	genome	human	Korea Centers for Disease Control &	Korea Centers for Disease Control &	Kim et al

								Prevention (KCDC), Center for Laboratory Control of Infectious Diseases, Division of Viral Diseases, Cheongju, Korea	Prevention (KCDC), Center for Laboratory Control of Infectious Diseases, Division of Viral Diseases, Cheongju, Korea	
BetaCoV/Nonthaburi/61/2020	EPI_ISL_403962	/	2020/1/8	Thailand	Bangkok	genome	human	Bamrasnaradura Hospital, Nonthaburi, Thailand	Department of Medical Sciences, National Institute of Health, Nonthaburi, Thailand	Pilailuk et al
BetaCoV/Nonthaburi/74/2020	EPI_ISL_403963	/	2020/1/13	Thailand	Bangkok	genome	human	Bamrasnaradura Hospital, Nonthaburi, Thailand	Department of Medical Sciences, National Institute of Health, Nonthaburi, Thailand	Pilailuk et al
BetaCoV/Shenzhen/SZTH-001/2020	EPI_ISL_406592	/	2020/1/13	China	Shenzhen	genome	human	Shenzhen Third People's Hospital, Shenzhen, China	Shenzhen Key Laboratory of Pathogen and Immunity, National Clinical Research Center for Infectious Disease, Shenzhen, China	Yang et al
BetaCoV/Shenzhen/SZTH-002/2020	EPI_ISL_406593	/	2020/1/13	China	Shenzhen	genome	human	Shenzhen Third People's Hospital, Shenzhen, China	Shenzhen Key Laboratory of Pathogen and Immunity, National Clinical Research	Yang et al

									Center for Infectious Disease, Shenzhen, China	
BetaCoV/Shenzhen/SZTH-003/2020	EPI_ISL_406594	/	2020/1/16	China	Shenzhen	genome	human	Shenzhen Third People's Hospital, Shenzhen, China	Shenzhen Key Laboratory of Pathogen and Immunity, National Clinical Research Center for Infectious Disease, Shenzhen, China	Yang et al
BetaCoV/Shenzhen/SZTH-004/2020	EPI_ISL_406595	/	2020/1/16	China	Shenzhen	genome	human	Shenzhen Third People's Hospital, Shenzhen, China	Shenzhen Key Laboratory of Pathogen and Immunity, National Clinical Research Center for Infectious Disease, Shenzhen, China	Yang et al
BetaCoV/Singapore/1/2020	EPI_ISL_406973	/	2020/1/23	Singapore	Singapore	genome	human	Singapore General Hospital, Singapore	National Public Health Laboratory, Singapore	Mak et al
BetaCoV/Taiwan/2/2020	EPI_ISL_406031	/	2020/1/23	Taiwan	Kaohsiung	genome	human	Centers for Disease Control, R.O.C., Taipei, Taiwan	Centers for Disease Control, R.O.C., Taipei, Taiwan	Yang et al
BetaCoV/USA/WA1-A12/2020	EPI_ISL_407214	MT020880	2020/1/25	USA	/	genome	human	WA State Department of Health	Pathogen Discovery, Respiratory Viruses Branch, Division of Viral Diseases, Centers	/

									for Dieases Control and Prevention	
BetaCoV/USA/WA1-F6/2020	EPI_ISL_407215	MT020881	2020/1/25	USA	/	genome	human	WA State Department of Health	Pathogen Discovery, Respiratory Viruses Branch, Division of Viral Diseases, Centers for Dieases Control and Prevention	/
BetaCoV/Wuhan/HBCDC-HB-01/2019	EPI_ISL_402132	/	2019/12/30	China	Wuhan	genome	human	Wuhan Jinyintan Hospital, Wuhan, China	Hubei Provincial Center for Disease Control and Prevention, Wuhan, China	Fang et al
BetaCoV/Wuhan/IPBCAMS-WH-01/2019	EPI_ISL_402123	MT019529	2019/12/23	China	Wuhan	genome	human	Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China	Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China	Ren et al
BetaCoV/Wuhan/IPBCAMS-WH-02/2019	EPI_ISL_403931	MT019530	2020/2/4	China	Wuhan	genome	human	NHC Key Laboratory of Systems Biology of Pathogens and Christophe Merieux Laboratory	National Genomics Data Center	Ren,L et al
BetaCoV/Wuhan/IPBCAMS-WH-	EPI_ISL_40393	MT019531	2019/12/30	China	Wuhan	genome	huma	Institute of	Institute of Pathogen	Ren et al

03/2019	0						n	Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China	Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China	
BetaCoV/Wuhan/IPBCAMS-WH-04/2019	EPI_ISL_403929	MT019532	2019/12/30	China	Wuhan	genome	human	Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China	Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China	Ren et al
BetaCoV/Wuhan/IPBCAMS-WH-05/2020	EPI_ISL_403928	MT019533	2020/2/4	China	Wuhan	genome	human	NHC Key Laboratory of Systems Biology of Pathogens and Christophe Merieux Laboratory	National Genomics Data Center	Ren,L et al
BetaCoV/Wuhan/IVDC-HB-01/2019	EPI_ISL_402119	/	2019/12/30	China	Wuhan	genome	human	National Institute for Viral Disease Control and Prevention, China CDC, Beijing, China	National Institute for Viral Disease Control and Prevention, China CDC, Beijing, China	Tan et al
BetaCoV/Wuhan/WH-01/2019	EPI_ISL_40679	/	2019/12/26	China	Wuhan	genome	huma	General Hospital of	BGI & Institute of	Chen et

	8						n	Central Theater Command of People's Liberation Army of China, Wuhan, China	Microbiology, Chinese Academy of Sciences & Shandong First Medical University & Shandong Academy of Medical Sciences	al
BetaCoV/Wuhan/WH-03/2019	EPI_ISL_406800	/	2020/1/1	China	Wuhan	genome	human	General Hospital of Central Theater Command of People's Liberation Army of China, Wuhan, China	BGI & Institute of Microbiology, Chinese Academy of Sciences & Shandong First Medical University & Shandong Academy of Medical Sciences	Chen et al
BetaCoV/Wuhan/WH-04/2019	EPI_ISL_406801	/	2020/1/5	China	Wuhan	genome	human	General Hospital of Central Theater Command of People's Liberation Army of China, Wuhan, China	BGI & Institute of Microbiology, Chinese Academy of Sciences & Shandong First Medical University & Shandong Academy of Medical Sciences	Chen et al
BetaCoV/Zhejiang/WZ-01/2020	EPI_ISL_404227	/	2020/1/16	China	Hangzhou	genome	human	Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China	Department of Microbiology, Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China	Chen et al

BetaCoV/Zhejiang/WZ-02/2020	EPI_ISL_404228	/	2020/1/17	China	Hangzhou	genome	human	Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China	Department of Microbiology, Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China	Zhang et al
Wuhan/WIV02/2019	EPI_ISL_402127	MN996527	2019/12/30	China	Wuhan	genome	human	Wuhan Jinyintan Hospital, Wuhan, China	Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan, China	Zhou et al
Wuhan/WIV04/2019	EPI_ISL_402124	MN996528	2019/12/30	China	Wuhan	genome	human	Wuhan Jinyintan Hospital, Wuhan, China	Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan, China	Zhou et al
Wuhan/WIV05/2019	EPI_ISL_402128	MN996529	2019/12/30	China	Wuhan	genome	human	Wuhan Jinyintan Hospital, Wuhan, China	Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan, China	Zhou et al
Wuhan/WIV06/2019	EPI_ISL_402129	MN996530	2019/12/30	China	Wuhan	genome	human	Wuhan Jinyintan Hospital, Wuhan, China	Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan, China	Zhou et al
Wuhan/WIV07/2019	EPI_ISL_402130	MN996531	2019/12/30	China	Wuhan	genome	human	Wuhan Jinyintan Hospital, Wuhan, China	Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan, China	Zhou et al

Wuhan-Hu-1/2019	EPI_ISL_402125	MN908947	2019/12/26	China	Wuhan	genome	human	unknown	National Institute for Communicable Disease Control and Prevention (ICDC), China CDC, Beijing, China	Zhang et al
Zhejiang/Hangzhou-1/2020	EPI_ISL_406970	MT039873	2020/1/20	China	Hangzhou	genome	human	Hangzhou Center for Disease and Control Microbiology Lab, Zhejiang, China	Hangzhou Center for Disease and Control Microbiology Lab, Zhejiang, China	Hua et al

Table S6 The integrated mutation information of all 67 published 2019-nCoV

Gisaid_epi_isl	Pos	Ref	Alt
EPI_ISL_402123	3778	A	G
EPI_ISL_402123	8388	A	G
EPI_ISL_402123	8987	T	A
EPI_ISL_402127	21316	G	A
EPI_ISL_402127	24325	A	G
EPI_ISL_402128	7016	G	A
EPI_ISL_402128	21137	A	G
EPI_ISL_402130	8001	A	C
EPI_ISL_402130	9534	C	T
EPI_ISL_402132	21656	T	A
EPI_ISL_403930	6996	T	C
EPI_ISL_403932	8782	C	T
EPI_ISL_403932	28144	T	C
EPI_ISL_403932	29095	C	T
EPI_ISL_403933	8782	C	T
EPI_ISL_403933	28144	T	C
EPI_ISL_403933	29095	C	T
EPI_ISL_403934	23569	T	C
EPI_ISL_403935	8782	C	T
EPI_ISL_403935	28144	T	C
EPI_ISL_403935	29095	C	T
EPI_ISL_403936	21707	C	T

EPI_ISL_403937	21707	C	T
EPI_ISL_404227	31	A	G
EPI_ISL_404227	583	C	T
EPI_ISL_406030	8782	C	T
EPI_ISL_406030	28144	T	C
EPI_ISL_406030	29095	C	T
EPI_ISL_406031	16188	G	T
EPI_ISL_406031	25964	A	G
EPI_ISL_406031	26144	G	T
EPI_ISL_406031	29877	A	T
EPI_ISL_406531	21707	C	T
EPI_ISL_406533	15324	C	T
EPI_ISL_406533	29303	C	T
EPI_ISL_406534	28291	C	T
EPI_ISL_406534	28854	C	T
EPI_ISL_406535	17373	C	T
EPI_ISL_406536	17373	C	T
EPI_ISL_406592	1648	C	T
EPI_ISL_406592	2169	T	C
EPI_ISL_406592	3801	A	C
EPI_ISL_406592	4643	GAAGAAGCTGCTCG	GGAGAAGCTGCTCC
EPI_ISL_406592	4727	GGTTATCTTACTT	GTATATCTTACTC
EPI_ISL_406592	5464	T	C
EPI_ISL_406592	6308	A	G
EPI_ISL_406592	6786	C	G

EPI_ISL_406592	6833	ATTAAA	AGTAAG
EPI_ISL_406592	8091	T	A
EPI_ISL_406592	8455	T	C
EPI_ISL_406592	12597	T	A
EPI_ISL_406592	15636	T	A
EPI_ISL_406592	19269	C	T
EPI_ISL_406592	20315	T	A
EPI_ISL_406592	24947	G	C
EPI_ISL_406592	25347	A	G
EPI_ISL_406592	26108	A	T
EPI_ISL_406592	26141	A	T
EPI_ISL_406592	26754	GGTGGA	GCTGGT
EPI_ISL_406592	28144	T	C
EPI_ISL_406592	29095	C	T
EPI_ISL_406593	8782	C	T
EPI_ISL_406593	28144	T	C
EPI_ISL_406593	29095	C	T
EPI_ISL_406594	27577	C	T
EPI_ISL_406594	28854	C	T
EPI_ISL_406595	709	G	A
EPI_ISL_406595	6846	T	C
EPI_ISL_406595	11707	A	G
EPI_ISL_406595	19959	A	C
EPI_ISL_406595	22621	GAACAGGAAGAGAATCAGCAACTGTGTTGCTG	GGACAGGAAGAGAATCAGCAACTGTGTTGCTT
EPI_ISL_406595	23569	T	C

EPI_ISL_406595	25645	T	C
EPI_ISL_406595	28716	C	T
EPI_ISL_406596	22661	G	T
EPI_ISL_406596	26144	G	T
EPI_ISL_406597	22661	G	T
EPI_ISL_406597	26144	G	T
EPI_ISL_406798	6968	C	A
EPI_ISL_406798	11764	T	A
EPI_ISL_406801	8782	C	T
EPI_ISL_406801	28144	T	C
EPI_ISL_406844	19065	T	C
EPI_ISL_406844	22303	T	G
EPI_ISL_406844	26144	G	T
EPI_ISL_406844	29749	ACGATCGAGTG	A
EPI_ISL_406862	241	C	T
EPI_ISL_406862	3037	C	T
EPI_ISL_406862	23403	A	G
EPI_ISL_406973	25060	A	G
EPI_ISL_407071	8782	C	T
EPI_ISL_407071	18488	T	C
EPI_ISL_407071	23605	T	G
EPI_ISL_407071	28144	T	C
EPI_ISL_407073	8782	C	T
EPI_ISL_407073	18488	T	C
EPI_ISL_407073	23605	T	G

EPI_ISL_407073	28144	T	C
EPI_ISL_407073	29596	A	G
EPI_ISL_407084	358	TGGAGACTCCGTGGAGGAGGTCTTA	T
EPI_ISL_407084	1912	C	T
EPI_ISL_407084	18512	C	T
EPI_ISL_407193	4402	T	C
EPI_ISL_407193	5062	G	T
EPI_ISL_407193	8782	C	T
EPI_ISL_407193	28144	T	C
EPI_ISL_407214	8782	C	T
EPI_ISL_407214	18060	C	T
EPI_ISL_407214	28144	T	C
EPI_ISL_407215	8782	C	T
EPI_ISL_407215	18060	C	T
EPI_ISL_407215	28144	T	C
EPI_ISL_407893	8782	C	T
EPI_ISL_407893	28144	T	C
MN975262	8782	C	T
MN975262	9561	C	T
MN975262	15607	T	C
MN975262	28144	T	C
MN975262	29095	C	T
MN985325	8782	C	T
MN985325	18060	C	T
MN985325	28144	T	C

MN994467	1548	G	A
MN994467	8782	C	T
MN994467	24034	C	T
MN994467	26729	T	C
MN994467	28077	G	C
MN994467	28144	T	C
MN994467	28792	A	T
MN994468	17000	C	T
MN994468	26144	G	T
MN997409	8782	C	T
MN997409	11083	G	T
MN997409	28144	T	C
MN997409	29095	C	T
MT019530	103	CTGCATGCTTAGTGCACTCACG	CAGCATGCCGAGTGCAGCCACA
MT019533	7866	G	T

The reference genomes we used was Wuhan-Hu-1 (GenBank accession number, NC_045512.2).

Reference

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